



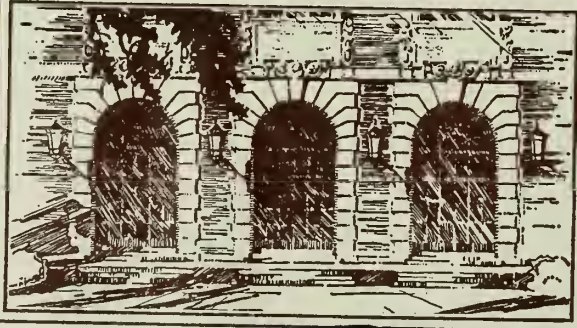
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Abstract Nos. 1-300

Vol. 10  
No. 1

# CARCINOGENESIS ABSTRACTS

National Cancer Institute

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • National Institutes of Health

# MEMORANDUM FOR THE RECORD

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PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain two-hundred abstracts and twenty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

*Carcinogenesis Abstracts* is normally published monthly. Volume IX covers the scientific literature published from July 1970 through June 1971. A cumulative subject and author index for Volume IX will be published shortly after the final regular issue. This journal is available free of charge to libraries and to individuals who have a professional interest in carcinogenesis. Requests for *Carcinogenesis Abstracts* from qualified individuals should include statements of their relationship to carcinogenesis research. All correspondence should be addressed as follows:

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# NOTE

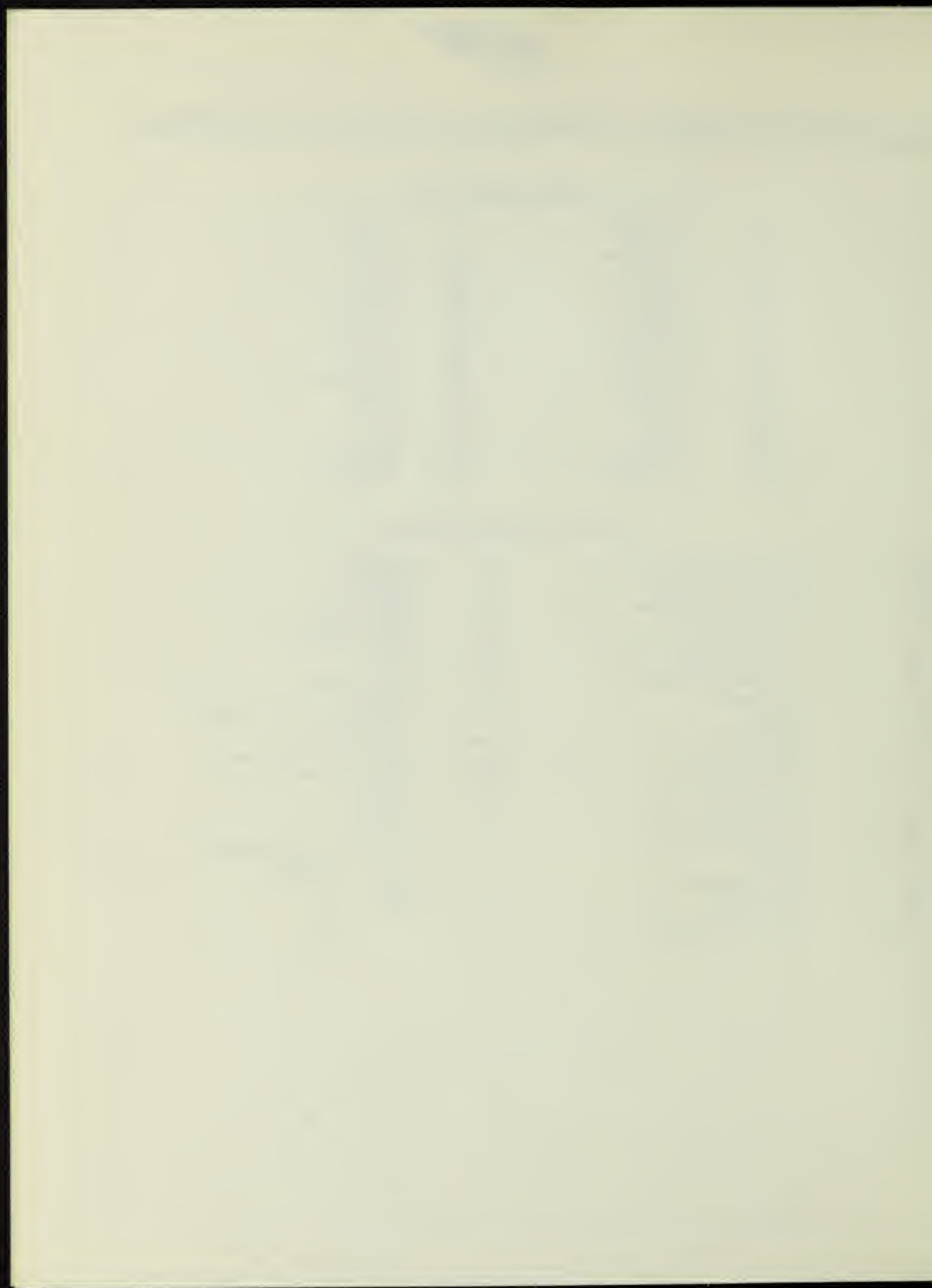
Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

## LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

## ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram ( $10^{-9}$ )
CNS	central nervous system	pg	picogram ( $10^{-12}$ )
cpm	counts per minute	p.O.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	U	unit(s)
kg	kilogram(s)	UV	ultraviolet
LD <sub>50</sub>	median lethal dose(s)	WBC	white blood cells (leukocytes), white blood count
m	meter(s)	wk	week
M	molar	wt	weight
mEq	milliequivalent(s)	yr	year(s)
mM	millimolar		
µM	micromolar		
mC, µC	milli-, microcurie(s)		



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## REVIEW

0001 THE ROLE OF IMMUNOSUPPRESSION IN THE GENESIS AND GROWTH OF MALIGNANT TUMORS. (E.) Reis, H. E. (Tumour Res. Polyclin., U. Ruhr, Essen, Germany). *German Med* 1(1):16-21, 1971.

Recent evidence linking experimental or iatrogenic immunosuppression and carcinogenesis was reviewed. Tumor growth and incidence were found to increase in animals given immunosuppressive treatments; rats in which the immune response was suppressed by thymectomy were more susceptible to tumorigenesis by polyoma virus than nonthymectomized rats. Even normal polyoma virus-resistant rat strains are rendered susceptible to the virus by thymectomy. Similar findings have been recorded for SV40 and adenovirus 12 in experiments with thymectomized rats. Antilymphocyte serum treatment of mice has also been shown to render mice highly susceptible to viral tumorigenesis. Animals undergoing immunosuppressive treatment with antilymphocyte serum and thymectomy have been shown in some studies to manifest an increased susceptibility to tumorigenesis by 3,4-benzo(a)pyrene and 3-methylcholanthrene. However, conflicting results have also been recorded and the conclusion that immunosuppression causes increased susceptibility to chemical carcinogens must remain provisional. Immunosuppressive treatment with azathioprine has been shown to increase the frequency of thymic lymphomas in treated mice; azathioprine is used as a postoperative medication in human organ transplant recipients. Organ transplant recipients generally, and especially recipients of kidney transplants, have been shown to be at a high risk of developing carcinoma. Immunosuppressive agents, including cortisone, azathioprine and antilymphocyte serum are commonly given to transplant recipients and it is widely thought that immunosuppression is directly related to the high incidence of cancer, especially lymphoreticular cancer, in transplant recipients. (86 references)

0002 THE POSSIBLE ROLE OF VIRUSES IN HUMAN CANCER. (E.) Epstein, M. A. (Dept. Path., U. Bristol, England). *Lancet* 1(7713):1344-1347, 1971.

The rise of the viral etiology theory of cancer has been reviewed. Early events which supported the thesis that viruses cause cancer in animals included the discovery of the Rous sarcoma virus, the discovery of the Bittner milk factor virus, and the discovery that mouse leukemia, a condition which is similar to human leukemia, is virus-induced. The discovery that feline lymphosarcoma virus caused malignant transformation of cat, dog, and human cells *in vitro* with equal ease silenced objectors to the theory who maintained that virus tumors in chickens and mice were irrelevant since these were populations genetically manipulated by man. DNA tumor viruses have recently been found; these viruses include the Lucke frog kidney virus (a herpes virus), the Marek's disease herpes virus and the herpes virus saimiri, which causes lymphoreticular tumors in marmosets and owl monkeys, species which are closely related to man. Although

no decisive evidence has been found that viruses cause cancer in humans, viruses have been associated with variety of human neoplastic conditions including mammary carcinoma, cervical carcinoma and Burkitt's lymphoma. (77 references)

0003 SPONTANEOUS AND VIRUS INDUCED TRANSFORMATION IN CELL CULTURE. (E.) Ponten, J. (Wallenberg Lab., U. Uppsala, Uppsala, Sweden). *Virology Monographs* 8:1-253, 1971.

In a 5-part book-length review, recent experimental findings concerning the growth, cytology, tumorigenicity and antigenicity of virally transformed and spontaneously transformed cell cultures were discussed. 1.) Three definitions of *in vitro* cell transformation were introduced: irregular growth transformation (marked by lack of contact-inhibition of cell membrane movement), unrestrained growth transformation (marked by deficient inhibition of mitosis), and infinite growth transformation (marked by the ability of cells to undergo an infinite number of divisions). Examples of the 3 types of transformation were described. 2.) Aspects of spontaneous transformation of non-hemopoietic cells were treated; the expression of each of the 3 types of cell transformation in hemopoietic cells was described. 3.) Spontaneous transformation of human lymphoid tissue or peripheral blood cells was discussed. 4.) A discussion of virus-induced transformation in cell cultures included mention of transformation induced by the DNA viruses (e.g., papova-adenovirus groups, polyoma virus and SV40) and by the RNA viruses (e.g., avian leukemia-sarcoma virus group, and murine leukemia-sarcoma virus group). 5.) In a concluding survey and discussion, the general characteristics of transformed cells were described and possible mechanisms for viral transformation of cells were reviewed. (1469 references)

0004 CARCINOGENICITY OF CHEMICAL IMMUNOSUPPRESSANTS AND OF CANCER CHEMOTHERAPEUTIC COMPOUNDS. (Ger.) Brock, N. (Hannover Med. Inst., Germany) and B. Schneider *Arzneimittelforschung* 21(4):435-446, 1971.

Investigations for carcinogenic effects elicited by antitumor agents and by immunosuppressants are discussed and a critical review of the work by Schmähl and Osswald is presented. According to the latter, carcinogenic effects are elicited by alkylating agents such as Dichlorethylamine, Mitomycin, Endoxan, Thio-tepa, Trenimon and Natulan as well as by radiotherapeutic procedures; degranol and myleran are considered to be slightly carcinogenic. Site and structure of the observed tumors appear to vary within a wide range. Antimetabolites such as methotrexate, 6-mercaptopurine or 5-fluorouracil and chemotherapeutic drugs, prepared from natural sources, such as colcemid, vinblastine and progesid appear to elicit no carcinogenic effects. (100 references)



- 0005 HEMATOSARCOMA IN BLACK AFRICA. (Fr.) Camain, R. (No affiliation) J. Linhard and M. Sankale. *Med Afrique Noire* 18(3):201-213, 1971.

The incidence of lympho- and myeloproliferative malignancies in Black Africa varies according to the districts but is generally higher than in temperate countries; leukemias, on the other hand, are less frequent in Africa. Malignancies, in decreasing order of incidence are: lymphosarcoma, reticulosarcoma, Hodgkin's disease, and multiple myeloma; these malignancies occur more frequently in men than in women and appear in lower age groups in Africa than in the temperate countries. Their localizations are identical with those in the temperate countries, except for a preferential occurrence in the facial areas of children of lympho- and reticulosarcomas. Burkitt's tumors develop selectively in the facial area but can also occur elsewhere; they develop from immature lymphoreticular cells. These tumors, resembling immunoblasts in cultures, occur only in humid and wooded areas whose mean temperature is higher than 15°C. The E.B. virus is often detected in Burkitt tumors maintained in culture. There is a possible relationship between Burkitt's tumors and nasopharyngeal carcinomas. Malarial infection may favor the development of these tumors as may the parodontoses often found in children in Black Africa. (21 references)

- 0006 MALIGNANT TUMORS OF THE LIVER AND PANCREAS IN BLACK AFRICA. (Fr.) Payet, M. (Inst. African Med. and Epid., Paris, France) and M. Sankale. *Med Afrique Noire* 18(3):215-226, 1971.

The incidence and geographical distribution in Black Africa of patients with primary carcinoma of the liver is reviewed. There have been no new major contributions to the etiology of this disease, but diagnostic techniques of some importance have been developed. These include evidence of alpha-1-feto-protein in about 3/4 of the cases and changes in serum enzymes (lactic dehydrogenase, 5'nucleotidase, and others). A minor role is attributed to aflatoxin in the etiology of liver malignancy. The Australia antigen, on the other hand, is frequently found in patients with primary liver cancer. Secondary carcinoma of the liver or pancreas is rare in Africa. (45 references)

- 0007 IMMUNOLOGIC ASPECTS OF CANCER. (E.) Sophocles, A. M. (Buffalo, N. Y.) and S. H. Nadler. *Surg Gynec Obstet* 133(2):321-331, 1971. (101 references)

- 0008 IMMUNITY TO MALIGNANT DISEASE IN MAN. (E.) Fairley, G. H. (No affiliation). *Sci Basis Med Ann Rev*:17-38, 1971. (101 references)

- 0009 IMMUNOLOGIC ASPECTS OF CARCINOMA OF THE COLON. (E.) Lamon, E. W. (U. Alabama Med. Ctr., Birmingham). *Alabama J Med Sci* 8(2):223-226, 1971. (21 references)

- 0010 IMMUNE ASPECTS OF NEUROBLASTOMA: CURRENT INFORMATION. (E.) Bill, A. H. (Children's Orthopedic Hosp., Seattle, Washington). *Amer J Surg* 122(2):142-147, 1971. (15 references)

- 0011 CELLULAR IMMUNITY AND BLOCKING ANTIBODIES TO TUMORS. (E.) Hellstrom, I. (U. Washington Med. Sch., Seattle) and K. E. Hellstrom. *J Reticuloendothel Soc* 10(1):131-136, 1971. (20 references)

- 0012 LIVER TUMOURS IN INFANCY AND CHILDHOOD. (E.) Keeling, J. W. (Hosp. Sick Children, London, England). *J Path* 103(2):69-85, 1971. (70 references)

- 0013 IMMUNOLOGY AND CANCER. (E.) Lauter, C. B. (Wayne State U. Sch. Med., Detroit, Mich.) and A. M. Lerner. *Bull Sinai Hosp Detroit* 19(3):131-133, 1971. (23 references)

- 0014 PRELEUKEMIA: A MODEL FOR INVESTIGATION INTO THE ETIOLOGY AND TREATMENT OF LEUKEMIA. (E.) Martin, W. A. (Kansas City, Kan.). *J Amer Osteopath Ass* 69(11):1104-1109, 1971. (43 references)

- 0015 ULCERATIVE COLITIS, AUTOIMMUNE EPITHELIOMA, AND COLONIC CANCER. (E.) Kronman, B. S. (No affiliation). *Cancer* 28(1):82-88, 1971. (84 references)

- 0016 IMMUNITY IN CANCER. (E.) Hunt, P. S. (Prince Henry's Hosp., Melbourne, Australia). *Aust New Zeal J Surg* 40(4):369-373, 1971. (46 references)

- 0017 BREAST-CANCER VIRUSES: MOUSE TO MAN -- ALMOST. (E.) Feller, W. F. (Georgetown U., Washington, D. C.). *Medical Opinion* 7(4):506-516, 1971. (No references)

- 0018 LEUKO- AND ONCOGENESIS IN THE LIGHT OF STUDIES ON THE METABOLISM OF MAGNESIUM AND ITS TURNOVER IN BIOGENESIS. (E.) Aleksandrowicz, J. (Med. Acad., Cracow, Poland), J. Blicharski, A. Dzigowska and J. Lisiewicz. *Acta Med Pol* 11(4):289-320, 1970. (48 references)

- 0019 BENIGNITY OF NEONATAL TUMORS AND CONCEPT OF CANCER REPRESSION IN EARLY LIFE. (E). Bolande, R. P. (Children's Hosp., Akron, O.). *Amer J Dis Child* 122(1):12-14, 1971. (33 references)
- 0020 HUMAN TUMOR IMMUNOLOGY. (E). Oettgen, H. F. (no affil.), L. J. Old and E. A. Boyse. *Med Clin N Amer* 55(3):761-785, 1971. (82 references)
- 0021 INTERFERON INDUCTION IN CANCER: WITH SOME OBSERVATIONS ON THE CLINICAL EFFECTS OF POLY I:C. (E). Young, C. W. (no affil.). *Med Clin N Amer* 55(3):721-728, 1971. (31 references)
- 0022 PROBLEMS IN THE STUDY OF ONCOGENS *IN VITRO*. (E). Sanders, F. K. (no affil.). *Med Clin N Amer* 55(3):653-665, 1971. (80 references)
- 0023 CANCER OF THE COLON AND RECTUM AND ADENOMATOUS POLYPS: A REVIEW OF EPIDEMIOLOGICAL FINDINGS. (E). Haenszel, W. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and P. Correa. *Cancer* 28(1):14-24, 1971. (22 references)
- 0024 OCCURRENCE OF MALIGNANCY IN IMMUNODEFICIENCY DISEASES: A LITERATURE REVIEW. (E). Gatti, R. A. (U. Minnesota Dept. Pediatrics, Minneapolis) and R. A. Good. *Cancer* 28(1):89-98, 1971. (129 references)
- 0025 PERSPECTIVES ON ONCOGENESIS: DOES IMMUNITY STIMULATE OR INHIBIT NEOPLASIA? (E). Prehn, R. T. (Inst. Cancer Res., Philadelphia, Pa.). *Reticuloendothel Soc* 10(1):1-16, 1971. (57 references)
- 0026 SYSTEMIC CARCINOGENS (N-NITROSO COMPOUNDS) AND SYNERGISTIC OR ADDITIVE EFFECTS IN RESPIRATORY CARCINOGENESIS. (E). Montesano, R. (Middlesex Hosp. Med. Sch., London, England). *Tumori* 56(6):335-344, 1971. (59 references)
- 0027 RADIATION INDUCED CANCER OF LARYNX AND PHARYNX. (E.) Cronin, J. (Manchester Royal Infirm., Manchester, England). *J Laryng* 85(6):621-622, 1971. (3 references)
- 0028 VIRUSES AND HUMAN CANCER: EVIDENCE FOR A VIRAL ETIOLOGY OF HUMAN GENITOURINARY NEOPLASMS. (E.) Fraley, E. E. (Hlth. Sci. Ctr., U. Minnesota, Minneapolis). *Minn Med* 5(7):499-502, 1971. (32 references)
- 0029 THE REACTIONS OF TISSUES TO MATERIALS. (E.) Williams, D. F. (Med. Physics Unit, U. Liverpool, Liverpool, England). *Biomed Engineering* 6(4):152-156, 1971. (28 references)
- 0030 FACTORS CONTRIBUTING TO THE "SUCCESS" OF ANTIGENIC TUMOURS. (E.) Alexander, P. (Chester Beatty Res. Inst., Belmont, Surrey, England). *Advances Exp Med Biol* 12:567-574, 1971. (19 references)
- 0031 RADIATION EFFECTS IN MAN: CURRENT VIEWS AND PROSPECTS. (E.) Mole, R. H. (Med. Res., Council Radiobiol. Unit, Harwell, Berkshire, England). *Health Phys* 20(5):485-490, 1971. (16 references)
- 0032 ARTIFICIAL SWEETENERS AS URINARY BLADDER CARCINOGENS. (E.) Bryan, G. T. (U. Wisconsin Med. Sch., Madison) and O. Yoshida. *Arch Environ Health* 23(1):6-12, 1971. (46 references)



0033 UTILIZATION OF NEWBORN MICE IN THE BIOASSAY OF CHEMICAL CARCINOGENS. (E).

Gargus, J. L. (Hazleton Lab., Inc., Falls Church, Va.) O. E. Paynter and W. H. Reese, Jr. *Toxic Appl Pharmacol* 15(3):552-559, 1969.

Newborn Swiss ICR random bred mice were given a single s.c. injection in the middle back area of 1 of 7 carcinogens: urethan, mesidine, N-nitrosodiethylamine, aflatoxin, nitrogen mustard, thiourea or DDT. Tumor promoters such as croton oil, dodecylbenzene and dimethyl sulfoxide were also administered to some animals as well as either saline, peanut oil or tricapyrin. A pulmonary tumor incidence of 2-14% was seen in mice 6 months after injection with saline or peanut oil. Doses of 1000 or 1500 mg/kg urethan produced incidences of 89.5-100% for adenomas in the lungs of treated mice; urethan dissolved in peanut oil produced a lower incidence of adenomas than urethan dissolved in saline. When nitrogen mustard (5 mg/kg) was injected into mice in saline, peanut oil or tricapyrin, lung adenomas appeared in 87% of mice given the carcinogen in saline, in 75% of mice given the carcinogen in peanut oil, and in 22% of mice given the carcinogen in tricapyrin. The tumor incidence produced by nitrogen mustard dissolved in tricapyrin was thought not to represent significant tumor inducing activity for this agent in this vehicle. N-Nitrosodiethylamine (50 mg/kg) produced an 80% lung adenoma incidence in mice treated with this carcinogen. Thiourea, mesidine, aflatoxin and DDT were inactive in the induction of lung adenomas in this study. Aflatoxin was administered in doses of 2.5 mg/kg, an amount less than the maximum tolerated dose. None of the tumor promoters -- croton oil, dodecylbenzene, or dimethyl sulfoxide -- were active in inducing lung adenomas in treated mice.

0034 HISTOLOGICAL AND ULTRASTRUCTURAL CHANGES IN EXPERIMENTAL HYPERPLASIA IN THE GUINEA-PIG. (E.) Cowan, M. A. (Med. Sch., U. Birmingham, England) and P. R. Mann. *Brit J Derm* 84(4):353-360, 1971.

A transient hyperplasia was produced in the epidermis of guinea pigs by topical application of n-hexadecane (0.01 ml) to shaved skin on the flanks; n-hexadecane was administered either once or 4 times on alternate days. Skin changes were visible at the ultrastructural level 1 day after treatment; epidermal cells, particularly those in the basal layer, showed intercellular edema and widening of the intercellular spaces. Basal cells showed marked intracellular vacuolation, and cells in the granular layer contained large numbers of keratinosomes. Epidermal abnormalities, including thickening of the epidermis, were maximal by day 3 after n-hexadecane treatment. At this point, some keratinocytes showed extensive cytoplasmic degeneration with breakdown of desmosomal contacts. By day 5 after treatment, the epidermis began to return to normal thickness and some of the ultrastructural abnormalities became less marked. Although infiltrating cells were still present in the epidermis,

disruption of the basal lamina had begun to reverse itself. Intracellular vacuolation in epidermal cells persisted to 7-10 days after n-hexadecane treatment. By day 14 the epidermis had returned to normal for the most part. Four separate administrations of n-hexadecane produced more ultrastructural abnormalities than did a single application of the compound; changes in the upper layers of the epidermis were more pronounced after 4 treatments than after 1 treatment.

0035 NEOPLASMS OF THE HEMATOPOIETIC SYSTEM IN NONHUMAN PRIMATES: REPORT OF ONE SPONTANEOUS TUMOR AND TWO LEUKEMIAS INDUCED BY PROCARBAZINE. (E.) O'Gara, R. W. (Nat'l. Cancer Inst., Bethesda, Md.), R. H. Adamson, M. G. Kelly and D. W. Dalgard. *J Nat Cancer Inst* 46(6):1121-1130, 1971.

A 5+yr-old male African green monkey (*Cercopithecus aethiops sabaeus*) was found at death to have developed reticulum cell sarcoma with invasion of liver, spleen and kidneys. The monkey had received no carcinogens. Myelogenous leukemia developed in a 17-month-old female rhesus monkey (*Macaca mulatta*) which had received procarbazine hydrochloride once/wk either s.c. in amounts of 50 mg/kg or orally in amounts of 10 mg/kg; both treatments dated from birth. Another female rhesus monkey, 5.5-yr-old, developed myelogenous leukemia after receiving from birth a total of 5.2 g of procarbazine hydrochloride s.c. and 31.1 g of the same agent orally.

0036 DOSE RELATED EFFECTS OF CYCASIN INDUCED RENAL AND HEPATIC TUMORS. (E.) Williams, P. D. (Roswell Park Mem. Inst., Buffalo, N.Y.) and G. P. Murphy. *Res Commun Chem Path Pharmacol* 2(4-5):627-632, 1971.

Male and female C-57 strain mice or Sprague-Dawley rats were given 1 or 2 s.c. injections of 0.25-2.5 mg cycasin and the ensuing development of renal and hepatic tumors was observed. Among mice, doses of cycasin from 0.5-2.5 mg proved lethal in all cases before the onset of tumors. Among mice given 0.25 mg doses of cycasin, 9 of 100 animals developed hepatomas; none of the tumor-bearing animals showed metastases and no correlation between tumor incidence and sex could be detected. Mice undergoing unilateral nephrectomy or ureteral ligation showed no increase in tumor development. Among rats given 0.5 mg doses of cycasin, 2 renal adenomas and no hepatic tumors developed in 20 intact animals, 1 renal adenoma and no liver tumors developed in 40 animals undergoing contralateral nephrectomy, and 2 hepatomas and no renal tumors developed in 40 animals undergoing contralateral ureteral ligation.

0037 INVESTIGATION OF THE COCARCINOGENICITY OF EXTRACTS FROM POLYPROPYLENE-MADE ARTICLES. (Rus.) Braun, D. D. (F. F. Erisman Res. Inst. Hyg., Moscow, U.S.S.R.). *Vop Pitan* 30(3):56-61, 1971.

The possible cocarcinogenic action in mice of water and fatty extracts from polypropylene-made articles was investigated. The extracts (obtained after 8-14 day contact with stabilized or nonstabilized polymer-made containers) were included in the daily diet of the experimental mice in lieu of water or fish liver oil. Three experimental groups, consisting of 50 male and 50 female mice each, were used. Group I consisted of control mice receiving untreated water and fish liver oil in their diet. Group II received extracts from stabilized polymer containers and group III received extracts from nonstabilized polymer containers. The mice were subjected to topical benzo(a)pyrene (in 0.6% benzene solution applied to intercostal skin) treatment once/wk starting 4 months after the beginning of the experiment and through the natural death of the animals. No differences were found between the control and treated groups with respect to the development and growth rate of papillomas, their malignant transformation or the life span of the animals. The investigation described is suggested as a model for the testing of other plastic articles.

- 0038 TUMOR INDUCTION BY PLASTIC FILMS: ATTEMPT TO CORRELATE CARCINOGENIC ACTIVITY WITH CERTAIN PHYSICO-CHEMICAL PROPERTIES OF THE IMPLANT. (E.) Carter, R. L. (Chester Beatty Res. Inst., London, England), F. J. C. Roe and R. Peto. *J Nat Cancer Inst* 46(6):1277-1289, 1971.

Sections of polyelectrolyte film, 20 mm square, were implanted s.c. in the right flank of rats; films were anionic (containing an excess of polyanions), cationic (containing an excess of polycations) or neutral (containing equal amounts of polyanions and polycations). No tumors were found in a sham-operated control group of rats. However, tumors were found in rats given implants of each of the 3 types of film. Of 16 rats given implants of neutral films, 1 developed sarcomas. Of 16 rats given implants of cationic film, 1 developed fibromas and 6 developed sarcomas. Of 16 rats given implants of anionic films, 3 developed sarcomas and none developed fibromas. Ectopic calcification marked the tissue response to anionic and cationic film implants but was seldom found in rats given neutral film implants.

- 0039 CARCINOGENIC ACTIVITY OF POLYCYCLIC PSEUDOAZULENES CONTAINING BOTH NITROGEN AND SULFUR HETEROCYCLES. (E.) Zajdela, F. (Radium Inst., U. Paris, Orsay, France), N. P. Buu-Hoi, P. Jacquignon, A. Croisy and F. Perin. *J Nat Cancer Inst* 46(6):1257-1260, 1971.

Mice of the strain XVII *nc/Z* were given 3 s.c. injections of 0.5 mg of each of 9 polycyclic pseudoazulenes derived from the nitrogen- and sulfur-containing heterocycles (1)benzothio-pyrano(4,3-*b*)indole and thieno(3',4':5,6)thiopyrano-(4,3-*b*)indole. Three compounds induced sarcomas: benzo(e)(1)benzothio-pyrano(4,3-*b*)indole, 6,13-dihydrobenzo-(e)(1)benzothio-pyrano(4,3-*b*)indole, and 2-chlorobenzo(e)(1)benzothio-pyrano(4,3-*b*)

indole. The first of these compounds induced sarcomas in 6 of 11 mice, the second in 24 of 28 mice and the third in 2 of 10 mice. All tumors induced were *in situ* fibroblastic sarcomas.

- 0040 TRANSPLACENTAL TOXICITY AND CARCINOGENICITY OF HEXAMETHYLENETETRAAMINE IN RATS. (It.) Della Porta, G. (Natl. Inst. Cancer Res. and Ther., Milan, Italy), J. R. Cabral and G. Parmiani. *Tumori* 56(6):325-334, 1970.

Carcinogenicity of hexamethylenetetraamine (HMT) in Wistar rats was investigated. Twelve female and 6 male rats were given 1% HMT in their daily drinking water starting 2 wk before mating. The female rats were kept under treatment during pregnancy and lactation. A similar group of 12 females and 6 males served as a control. Twelve treated females and 11 controls gave birth to 124 and 118 babies resp.; of these offspring, 24 of each sex were subjected to 1% HMT in drinking water treatment up through the 20th wk of age or were kept under no treatment. In another experiment rats were given 1% HMT in the drinking water for 3 successive generations, up to 40 wk of age in the first 2 and through 20 wk of age in the 3rd generation. In addition, a group of 16 male and 16 female descendants of 2% HMT-treated parents were given 2% HMT for 50 wk. No evidence for HMT carcinogenicity could be found in any of the experimental groups after a 2-yr observation period.

- 0041 EFFECT OF DIET ON N,N-DIMETHYL-*p*-(*m*-TOLYLAZO)ANILINE CARCINOGENESIS IN RATS. (E.) Mulay, A. S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and R. W. O'Gara. *Proc Soc Exp Biol Med* 137(3):907-910, 1971.

Male and female rats of the Osborne-Mendel, NIH black, or Marshall strains were fed either commercial or protein- and riboflavin-deficient diets; rats in both groups were given N-N-dimethyl-*p*-(*m*-tolylazo)aniline (3'-Me-DAB) in their food in concentrations of 0.06, 0.09, 0.098, 0.12 or 0.18%. Male rats given the conventional diet and 3'-Me-DAB (0.06%) had a liver tumor incidence of 40% whereas those given 0.09 and 0.098% concentrations of 3'-Me-DAB had a hepatoma incidence of 67 and 100%, resp. Among conventionally-fed female rats given 0.06, 0.09 and 0.12% concentrations of 3'-Me-DAB the hepatoma incidence was 0, 33, and 100%, resp. Both male and female rats on the deficient diet developed tumors in 100% of the cases with the 0.06% 3'-Me-DAB diet. Lung metastases were found in up to 83% of rats given conventional diet and 3'-Me-DAB; in contrast, the highest incidence of metastases found in the diet-deficient group was 57%. Liver tumors in all rats were similar histologically; lesions ranged from well-differentiated hepatomas to poorly-differentiated hepatocellular carcinomas.

- 0042 BIOCHEMICAL EFFECTS OF AFLATOXIN IN PIGS. (E.) Gumbmann, M. R. (J. S. Dept. Agriculture, Albany, Calif.) and S. N. Williams. *Toxic Appl Pharmacol* 15(2):393-404, 1971.



Young pigs were maintained on diets supplemented with preparations of aflatoxin; B<sub>1</sub> aflatoxin was added to the regular feed in amounts of 2, 5, 8, 51, 105, 233, 450, 615 or 810 parts per billion (ppb). Biochemical changes in liver and blood of aflatoxin-treated pigs were investigated. After 88 days of feeding with 233 ppb aflatoxin, significant changes were seen in the blood; plasma alkaline phosphatase was elevated to 14.8 King-Armstrong U/100 ml (in pigs given 8 ppb aflatoxin, alkaline phosphatase activity was at 9.8 U/100 ml). The levels of nonprotein nitrogen and urea nitrogen in the blood were both decreased in pigs given 233 ppb aflatoxin; the latter factor was at 21.3 mg/100 ml in pigs given 8 ppb aflatoxin and at 15.0 mg/100 ml in pigs given 233 ppb aflatoxin. Other blood factors which decreased with aflatoxin supplemented diets included plasma albumin, albumin:globulin ratio and adenine nucleotides. Serum glutamic-oxaloacetic transaminase and isocitric dehydrogenase were elevated in animals given aflatoxin. In livers of aflatoxin-treated pigs, alkaline phosphatase activity showed a 40% increase as compared to controls not fed aflatoxin. Glutamic-oxaloacetic transaminase, isocitric dehydrogenase, lipid content, vitamin A, glycogen and total nitrogen decreased in livers of pigs given the higher (i.e., > 233 ppb) concentrations of aflatoxin. No effects were produced in the progeny of mated pairs of pigs fed with a diet containing 450 ppb aflatoxin.

- 0043 THE EFFECT OF AFLATOXIN B<sub>1</sub>, AFLATOXIN B<sub>2</sub> AND STERIGMATOCYSTIN ON NUCLEAR DEOXYRIBONUCLEASES FROM RAT AND MOUSE LIVERS. (E.) Pitout, M. J. (South African Med. Res. Council, Pretoria), H. A. McGee and J. C. Schabort. *Chem Biol Interact* 3:353-361, 1971.

Male rats and male albino mice were given injections of aflatoxin B<sub>1</sub> (1/5 LD<sub>50</sub> for rats and 2.5 mg/kg for mice), aflatoxin B<sub>2</sub> or sterigmatocystin and the effects of these carcinogens on liver cell nuclear DNase activity rates were observed. Aflatoxin B<sub>2</sub> had little effect on either acid or alkaline DNase (DNase types II and I, resp.). However, aflatoxin B<sub>1</sub> markedly increased DNase II in rat liver; by 20 days after administration of aflatoxin B<sub>1</sub>, DNase II increased to 880% of control values. Aflatoxin B<sub>1</sub> did not affect DNase I levels in rat liver. Sterigmatocystin did not appreciably change the level of either DNase in rat liver. Neither aflatoxin B<sub>1</sub>, aflatoxin B<sub>2</sub> or sterigmatocystin produced changes in DNase I or II in mouse liver. In experiments designed to determine the effect of aflatoxins and sterigmatocystin on rat liver nuclear DNase I and II *in vitro*, it was found that aflatoxin B<sub>1</sub> had no effect on either DNase in cultured cells; *in vitro* investigations could not be performed with sterigmatocystin due to its poor solubility.

- 0044 MUTAGENIC ACTIVITIES OF AFLATOXIN B<sub>1</sub> AND G<sub>1</sub> IN *Neurospora crassa*. (E.) Ong, T-M. (Dept. Biol. Sci., Illinois State U., Normal). *Molec Gen Genet* III(2):159-170, 1971.

Vegetative tissues or conidia of *Neurospora crassa* were exposed to varying amounts of either aflatoxin B<sub>1</sub> or aflatoxin G<sub>1</sub> and the mutagenicity of the 2 compounds for cells in these tissues was assessed by the adenine-3 (*ad* 3) test system. Neither compound produced forward mutations in resting conidia. However, 4<sup>th</sup> µg/ml aflatoxin B<sub>1</sub> produced a mutation frequency in vegetatively growing *N. crassa* cells of 87.0 x 10<sup>-6</sup> (the spontaneous mutation frequency was 0.4 x 10<sup>-6</sup>). The maximum frequency of forward mutations induced by aflatoxin G<sub>1</sub> was 12.3 x 10<sup>-6</sup>. Both aflatoxin B<sub>1</sub> and aflatoxin G<sub>1</sub> induced similar frequencies of mutation types including leaky mutants, multi-locus deletion and allelic complementation. The *ad*-3 mutants produced by the aflatoxins included base-pair transitions and frameshifts. The aflatoxins induced higher frequencies of *ad*-3 mutants than did 2-methoxy-6-chloro-9-(3-(ethyl-2-chloro-ethyl)aminopropylamino)-acridine, and induced lower frequencies of mutants than did nitrous acid and 2-aminopurine.

- 0045 TOXIC EFFECTS ON TROUT, RATS, AND MICE OF T-2 TOXIN PRODUCED BY THE FUNGUS *Fusarium tricinctum* (Cd.) SNYD. ET HANS. (E.) Marasas, W. F. O. (Dept. Plant Path., U. Wisconsin, Madison), J. R. Bamberg, E. B. Smalley, F. M. Strong, W. L. Ragland and P. E. Degurse. *Toxic Appl Pharmacol* 15(2):471-482, 1971.

Rainbow trout fingerlings were fed a diet containing toxin produced by the fungus *Fusarium tricinctum*; the toxin, 4,15-diacetoxy-8-(3-methylbutyryloxy)-12,13-epoxy-Δ<sup>9</sup>-trichothecene-3-ol (T-2 toxin) was introduced into food in amounts of 200 or 400 ppb. After 9 and 12 months on the treated food, trout showed an increase of weight and length as compared to controls fed a normal diet. No neoplasia or hyperplasia were found in livers of trout fed the toxic diet. After a period of feeding with 200 or 400 ppb of T-2 toxin, some trout were given acute dietary doses of toxin (2,4 or 8 mg/kg); although fish given acute doses of toxin sloughed off their intestinal mucosa, no other differences were seen between trout fed acute doses of toxin and trout given lighter doses. In a related experiment, rats were fed 5 or 15 ppm of T-2 toxin for 3 wk; these rats showed growth retardation and developed inflamed areas around the nose and mouth. The livers of rats fed T-2 toxin showed some cytoplasmic degeneration. No overt hepatomas were seen in livers of any of the toxin-fed rats. Topical application of toxin to rat dorsal skin produced a marked inflammatory reaction with necrosis and extensive tissue damage. T-2 toxin was applied topically to the backs of mice with or without subsequent application of croton oil. No papillomas appeared in any of the mice so treated. However, 2 of 20 mice given topical 7,12-dimethylbenz(a)-anthracene followed by weekly applications of T-2 toxin developed papillomas.

- 0046 CHROMOSOME PATTERNS IN RAT HEPATOCYTES DURING N-2-FLUORENYLACETAMIDE CARCINOGENESIS. (E.) Becker, F. F. (New York U. Sch.



Med., N.Y.), R. A. Fox, K. M. Klein and S. R. Wolman. *J Nat Cancer Inst* 46(6):1261-1269, 1971.

Karyotype studies were performed on hepatic nodules induced in the livers of rats by feeding for 9 or 12 wk with a 0.06% concentration of N-2-fluorenylacetamide (2-FAA); chromosomal patterns of hepatic nodules were compared with patterns of chromosomes in normal rat liver cells and with patterns in hepatocellular carcinomas. Metaphase hepatocytes from normal rat liver showed no chromosomal aberrations; livers from rats weighing 125 g were tetraploid in 1% of mitoses or less and livers from rats weighing 400 g were tetraploid in 5-10% of mitoses. Nodular hepatocytes from rats given 2-FAA were tetraploid in less than 1% of cases; in rats fed 2-FAA for 9 wk, 1-10 cells of 120-1,350 cells observed showed chromosomal gaps and breaks and up to 41 cells showed chromosomal associations. Hepatocellular carcinomas, arising 2-8 months after termination of 2-FAA feeding, showed bimodal populations of cells in mitosis; there was a sharp diploid mode and another mode of cells in the sub-tetraploid range. Abnormal metacentric or large telocentric chromosomes were found in many non-diploid cells in all tumors. No clear correlation could be discerned between the chromosomal patterns of the supposedly premalignant nodules and the patterns of the liver cell carcinomas.

0047 DNA MEASUREMENT ON CELL NUCLEUS OF NORMAL LIVER, ADENOMA, AND HEPATOMA IN MICE: HISTOLOGIC FEATURES. (E.) Inui, N. (Cancer Inst., Tokyo, Japan), S. Takayama and N. Kuwabara. *J Nat Cancer Inst* 47(1):47-58, 1971.

Male strain ICR mice were maintained for 27 wk on a diet consisting of 0.025% N,N'-2,7-fluorenylenebisacetamide, and when liver tumors were fully developed microspectrophotometric techniques were used to estimate the DNA content of cell nuclei of liver carcinomas, liver adenomas, intermediate tumors and normal liver and kidney. Normal liver cell nuclei showed modal peaks of DNA in the basic diploid and tetraploid ranges with limited variation around these modes. Kidney cell DNA showed a similar range of ploidies. Of 20 liver adenomas 19 were near diploid and 1 was near triploid, while of 16 intermediate tumors, 11 were near diploid, 1 was hyperdiploid, 2 were triploid and 2 were tetraploid. Of 23 liver carcinomas, 7 were diploid, 5 were triploid, 5 were tetraploid, 5 were over-tetraploid and the chromosomal mode of 1 could not be determined.

0048 LOCALIZATION OF ACID PHOSPHATASE ACTIVITY IN WELL-DIFFERENTIATED HEPATOCELLULAR CARCINOMA 146. (E.) Essner, E. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.) and M. D. Reuber. *J Nat Cancer Inst* 47(1):25-33, 1971.

Electron microscopic studies were carried out on a well-differentiated transplantable hepatocellular carcinoma induced in a rat by N-2-fluorenyldiacetamide; the localization of acid phosphatase in the tumor cells was investigated. Tumor cells had a

well-developed Golgi apparatus showing pericanalicular and perinuclear orientation, and many peroxisomes and lysosomes. Ultrastructurally, Golgi apparatus consisted of 4 or 5 flattened saccules. Peroxisomes were often seen near these saccules, where they were often associated with endoplasmic reticulum. After incubation for acid phosphatase activity, the reaction product was seen to be localized in dense bodies resembling lysosomes, in Golgi saccules, and in the cisternae of unusual, elongated, smooth-surfaced structures which were often seen near peroxisomes.

0049 CARCINOGENIC ACTION OF 2,7-DIACETYLAMINO-FLUORENE ON THE STOMACH OF RATS WITH EXPERIMENTAL GASTRIC ULCER. (E.) Kowalewski, K. (Surg.-Med. Res. Inst., U. Alberta, Edmonton, Canada) and E. F. Todd. *Scand J Gastroent* 6(4):323-328, 1971.

Penetrating gastric ulcers were produced in the stomachs of male rats by electrothermocautery. These rats and uninjured controls were fed a diet containing 0.25 g/kg of a known carcinogen, 2,7-diacetylaminofluorene (2,7-DAAF), following thermocautery. Twenty of 50 rats showed precancerous stomach lesions after 30-44 wk of observation; only 3 of 53 controls showed precancerous lesions. Seven of 50 rats developed gastric adenocarcinomas whereas none of the controls showed carcinomas. It was concluded that the contact of the chemical carcinogen 2,7-DAAF with injured, healing gastric mucosa enhanced the malignant transformation of gastric cellular elements.

0050 INTERACTIONS OF AZODYE CARCINOGENS AND AZODYE CARCINOGEN CONJUGATES WITH SPECIFIC PROTEINS IN THE RAT LIVER. (E.) Ketterer, B. (Middlesex Hosp. Med. Sch., London, England), D. Beale, G. Litwack and J. F. Hackney. *Chem Biol Interact* 3:285-286, 1971.

Some physical and chemical properties of azodye (i.e., N, N-dimethyl-4-aminoazobenzene and derivatives)-binding proteins of the soluble cytoplasm of the liver were described. Apparently, some of the bound azodye is in fact strongly bound azodye conjugate. The azodye-binding proteins include a basic protein and low molecular wt protein. The basic protein has been shown to bind metabolites of the skin carcinogen 3-methylcholanthrene. The molecular wt of the basic protein is 45000, and that of the low molecular wt protein is 14000. In the basic protein, the amino acid residue which binds the azodye is Cys; amino acid analysis of the performic acid-oxidized azodye conjugate reveals that its constituents are Glu,  $\text{CySO}_3\text{H}$  and Gly. The amino acid which binds the azodye in the low molecular wt protein is Met.

0051 HISTOCHEMICAL STUDY OF THE "ADRENOCORTICAL LIPID HYPERPLASIA" INDUCED IN RATS BY ANILINE. (E.) Horvath, E. (Inst. Med. Exper. Surg.,

U. Montreal, Quebec, Canada), K. Kovacs and E. Yeghiayan. *Acta Histochem* 39(1):154-161, 1971.

Female rats were given daily s.c. injections of 30 mg aniline for 2, 7 or 14 days; no marked alterations were seen in adrenals of rats given 2 aniline treatments. Adrenals in rats given 7 or 14 treatments were enlarged and showed disrupted cortical zonation. A mild or moderate inflammatory reaction accompanied the morphological changes in the adrenals of these rats. Sudanophilic lipids and cholesterol concentrations were increased in rats given 7 or 14 aniline injections and succinic dehydrogenase, lactic acid dehydrogenase and steroid-3 $\beta$ -ol dehydrogenase concentration were decreased. The results indicate that aniline may interfere with corticosteroidogenesis at the adrenal level.

0052 BENZIDINE-INDUCED LIVER TUMORS IN MICE.  
(*Rus.*) Prokof'yeva, O. G. (N. N. Petrov Res. Inst. Oncol. Leningrad, U.S.S.R.) *Vop Onkol* 17(5):61-64, 1971.

Benzidine administered to 181 C3HA mice (6 mg s.c. once/wk for 8 or 13 months) induced tumors in 69% of the animals. The first tumor developed 16 months after the beginning of the experiment; at this time, 46 mice were still alive, of which 22 each received 210 mg and 24 each received 336 mg of benzidine. Of 21 mice that survived for 28 months 31 developed hepatocellular carcinoma and 2 developed malignant adenocarcinoma of the lung. The evidence of the hepatotropic effects of benzidine in C3HA mice is emphasized.

0053 DIMETHYLBENZANTHRACENE BINDING TO EPIDERMAL CHALONE. (*E.*) Bishai, I. S. M. (Banting Inst., U. Toronto, Toronto, Canada), M. A. Moscarello and A. C. Ritchie. *Nature* 232(5306):114-116, 1971.

The binding of 7,12-dimethylbenz(a)anthracene-9-<sup>14</sup>C (DMBA-<sup>14</sup>C) to epidermal chalone was investigated in order to study the role played by chalone in skin carcinogenesis. DMBA-<sup>14</sup>C in doses of 70-100  $\mu$ g/mouse (50  $\mu$ C/1.96 mg) or anthracene-<sup>14</sup>C (55-70  $\mu$ g/mouse) 180  $\mu$ C/mg) in acetone were applied to the backs of 10-12-wk-old Swiss Webster mice with a special micropipette. The animals were killed after 6, 24 or 48 hr and the treated epidermis was extracted and fractionated with pre-cooled 96% ethanol to final concentrations of 55, 70 and 80% (w/v) resp. The binding of anthracene appeared to be negligible in all fractions whereas the binding of DMBA-<sup>14</sup>C was maximal in the fraction precipitated with between 70 and 80% alcohol, 24 hr after topical application of the carcinogen. Acrylamide disc electrophoresis revealed 2 light bands in the material from DMBA-<sup>14</sup>C-treated animals, which were not present in control or anthracene-treated skin preparations. The highest specific activity was encountered after DMBA-<sup>14</sup>C treatment in the fraction of water-soluble protein precipitated with 70-80% alcohol. This fraction has been

reported to contain more than 80% of the epidermal chalone. The DMBA-<sup>14</sup>C binding to this fraction seemed to be covalent. Since the 70-80% fraction is very active in the mitotic control *in vitro* and *in vivo*, the protein to which the carcinogen binds could be chalone; if so, chalone may be of considerable importance in carcinogenesis.

0054 A TRANSPLANTABLE METASTASIZING TUMOR STRAIN OF SYRIAN HAMSTERS. (*Rus.*) Kiseleva, N. S. (Inst. Exp. Clin. Oncol., Moscow, U.S.S.R.) *Vop Onkol* 17(5):64-69, 1971.

Specific features of metastases from a transplantable dimethylbenz(a)anthracene-induced Syrian hamster sarcoma maintained in tissue culture for 123 generations were investigated. Tumor tissue was inoculated s.c. to 33 1-month-old Syrian hamsters (0.2 ml of a 25% suspension in physiological solution). The tumor strain elicited 100% transplantability and a fast growth rate after a latency period of 4-6 days. The neoplastic tissue consisted of large polymorphous cells with vacuolated nuclei and high mitotic activity; the stroma was poor and of rather fibrillar consistency. Metastases located in the axillary lymph nodes were observed in 29 (90.6%) of 32 tumor-bearing hamsters 10 days following inoculation. Bilateral metastases were found in the pararenal (50% incidence) and in the lumbar lymph nodes (53% incidence) 15 days following inoculation. Twelve hamsters (37%) were found to have developed metastases in the lung and, later, 11 hamsters developed metastases in the inguinal, 11 in the cervical and 9 in the paratracheal lymph nodes. No metastases were seen in the liver, kidney or spleen. Three morphologically distinct stages could be established for the development of metastases at the respective sites: 1) a stage of subcapular growth of the tumor within the lymph node; 2) a stage of "break-through" of the tumor mass directed towards the central region of the lymph node with a gradual substitution of the lymphoid tissue by tumor tissue; 3) a stage of total substitution of the lymphoid tissue by tumor tissue whereby morphological integrity of the lymph node capsule is maintained. The transplantable Syrian hamster sarcoma is thought to provide an experimental model for lymphatic metastases.

0055 ENHANCEMENT OF THE CARCINOGENICITY OF 7,12-DIMETHYLBENZ(a)ANTHRACENE THROUGH REPLACEMENT OF HYDROGEN BY DEUTERIUM: A NEW BIOLOGICAL ISOTOPE EFFECT. (*E.*) Buu-Hoi, N. P. (Nat. Ctr. Sci. Res., Paris, France) and N. B. Giao. *Naturwissenschaften* 58(7):371, 1971.

Male and female Swiss strain mice were given s.c. injections of 1.5 mg 7,12-dimethylbenz(a)anthracene-*d*<sub>16</sub>, a form of the carcinogenic hydrocarbon in which 99% of the hydrogen is in the form of deuterium; controls were given similar doses of non-deuterated dimethylbenz(a)anthracene. Of 31 male mice given the deuterated compound, 29 developed sarcomas and of 26 females, all developed sarcomas.



The average latencies for tumor development among male and female mice given 7,12-dimethylbenz(a)anthracene- $d_{16}$  were 131 and 90 days, resp. Of 20 male mice given the conventional compound, 15 developed sarcomas and of 20 females, 16 developed tumors; the male and female latencies in this group of mice were 142 and 140 days, resp. Tumors developed by rats given conventional and deuterated compounds were fibroblastic sarcomas. Apparently, the deuterated compound was significantly more sarcomagenic than the conventional compound.

0056 THYMECTOMY AND ITS EFFECT ON CHEMICALLY INDUCED SUBMANDIBULAR NEOPLASMS. (E.)

Sheehan, R. (Tufts U. Sch. Dental Med., Boston, Mass.) and G. Shklar. *J Dent Res* 50(4):981, 1971.

Ten thymectomized and 10 nonthymectomized male rats were implanted with pellets of 7,12-dimethylbenz(a)anthracene in the submaxillary gland. Seventeen wk later, the rats were killed and it was found that the nonthymectomized animals had developed cystic lesions adjacent to the carcinogen pellets and had developed well differentiated papillary carcinomas within the cyst walls. In thymectomized rats given carcinogen pellets, epidermoid carcinomas developed in the cystic lesions in all rats but the carcinomas were larger, more anaplastic and more deeply invasive than in nonthymectomized rats. Fibrosarcomas developed in 40% of thymectomized rats and in none of the nonthymectomized rats.

0057 EFFECT OF FLUOROURACIL ON CARCINOGENESIS OF RAT SUBMANDIBULAR GLANDS. (E.) Shklar,

G. (Tufts U. Sch. Dental Med., Boston, Mass.) and S. Turbiner. *J Dent Res* 50(4):985, 1971.

Male and female rats were given implanted pellets of pure 7,12-dimethylbenz(a)anthracene in the right submandibular gland; 16 of the treated animals were also given daily s.c. injections of 3.5 mg fluorouracil, an antimetabolite. In rats given carcinogen pellets alone, dysplasia developed associated with cyst formation peripheral to regions of coagulative degeneration; dysplasia developed within 8 wk after pellet implantation in rats not given fluorouracil. By 10 wk after implantation, these rats had begun to implantation, rats in this group had begun to develop carcinoma. In rats given fluorouracil as well as carcinogen pellet, the process of carcinogenesis was accelerated; dysplasia developed in 6 wk and papillary epidermoid carcinomas developed in 10 wk.

0058 POTENTIATION OF BENZO(a)PYRENE TUMORIGENESIS IN THE PROGENY OF FEMALE HAMSTERS INJECTED WITH FREUND'S INCOMPLETE ADJUVANT. (E.)

Pinkerton, H. (St. Louis U. Sch. Med., St. Louis, Mo.), P. I. S. Liu and E. S. Holtwick. *Proc Soc Exp Biol Med* 137(2):461-463, 1971.

Pregnant hamsters were injected s.c. in the right lower back with 1.0 ml Freund's incomplete adjuvant; after parturition, offspring were given 3 times weekly s.c. injections of 0.25 ml benzo(a)pyrene (BP) in the right middle back area. Offspring of adjuvant-treated hamsters showed a higher incidence of BP-induced tumors than did offspring of untreated hamsters. By 79 days after the first BP treatment, 28% of offspring of adjuvant-treated hamsters had tumors and 12% of offspring of untreated hamsters had tumors. The final tumor incidences of BP-induced tumors among adjuvant treated and untreated hamster offspring were 84% and 65%, resp. The average tumor weight among offspring of adjuvant-treated hamsters was 6.1 g, while the average tumor weight among offspring of untreated hamsters was 1.7 g.

0059 TRANSFORMATION OF RAT AND HAMSTER EMBRYO CELLS BY EXTRACTS OF CITY SMOG. (E.)

Freeman, A. E. (Microbiological Associates, Inc., Bethesda, Md.), P. J. Price, R. J. Bryan, R. J. Gordon, R. V. Gilden, G. J. Kelloff and R. J. Huebner. *Proc Nat Acad Sci USA* 68(2):445-449, 1971.

Normal and Rauscher leukemia virus-infected cultures of rat embryo cells were exposed to benzo(a)pyrene alone and together with particulate residues filtered from smog in the air of a large city in the United States. Smog residues were administered to the culture in so-called " $\mu$ g U"; a  $\mu$ g U contained about 43,000  $\mu$ g of residue of which about 1  $\mu$ g was benzo(a)pyrene. Virus-free rat embryo cell cultures were not transformed by doses of smog residue up to 0.007  $\mu$ g U/ml or by benzo(a)pyrene doses up to 1.0  $\mu$ g/ml. Rat embryo cell cultures infected with Rauscher virus were transformed by 0.0007  $\mu$ g U/ml of smog residue and by 0.4  $\mu$ g/ml of benzo(a)pyrene. When normal hamster embryo cells and hamster cells infected with a hamster C-type RNA virus were exposed to benzo(a)pyrene alone or together with smog residues, transformation occurred in virus-free cultures exposed to 0.007  $\mu$ g U but not in cultures exposed to 0.0007  $\mu$ g U. Virus-infected cultures were transformed by both doses of smog residue. When cells from cultures of rat and hamster cells transformed by smog residues were injected into rats and hamsters no tumors were induced.

0060 HISTOGENESIS OF METHYLCHOLANTHRENE-INDUCED MURINE CERVICAL CANCER. (E.) Graham,

C. E. (Yerkes Reg. Primate Ctr., Emory U., Atlanta, Ga.). *Oncology* 25(3):269-282, 1970.

To investigate the exact point of origin of experimentally induced cervical squamous carcinomas in the mouse, cotton threads impregnated with beeswax and/or 3-methylcholanthrene were inserted into the cervical canal and one of the uterine horns of female strain C3H/HeJ mice. Mice were killed after 4 and 6 wk. Invasive squamous carcinomas occurred in 58% of all methylcholanthrene-treated mice. The initial response of the uterus to the implantation

of a plain or carcinogen-treated thread was proliferation of the cervical squamous stratified epithelium and its upgrowth into the uterus; this proliferation replaced columnar cells and displaced the squamocolumnar junction to the cranial region of the cervix. In treated mice, squamous carcinomas always occurred in an area of squamous stratified epithelium. Thirty percent of the mice with carcinomas had lesions occurring below the original squamocolumnar junction, while 40% had lesions occurring at the area of the original junction and 81% had lesions occurring above the original junction in the region of the newly-formed stratified epithelium. It was concluded that all the squamous tumors induced by the methylcholanthrene-treated threads originated from cervical stratified epithelium.

- 0061 THE EXTRACELLULAR SPACE IN EXPERIMENTAL BRAIN TUMORS. (E.) Kobayashi, T. (State U. New York Sch. Med., Buffalo, N. Y.) and L. Bakay. *Acta Neurol Scand* 47(3):307-314, 1971.

Male C3H strain mice were given implanted pellets of 3-methylcholanthrene intracranially to induce tumors; tumors which developed included meningeal sarcomas, astrocytomas, oligodendromas and glioblastomas. When tumors had developed, radioactive tracers including  $C^{14}$ -sucrose,  $C^{14}$ -inulin and  $H^3$  inulin were injected i.v. into tumor-bearing mice in doses ranging from 4-100  $\mu$ C/mouse; the incorporation of these extracellular markers by tumor tissue was observed. All tumors were edematous compared to normal brain tissue in terms of water content; the mean water content of tumors was 80.89% while that of normal brain tissue was 74.57%. The concentration of all radioactive molecules was higher in tumor tissue than in normal brain tissue. In astrocytomas, the tumor/brain ratio of  $C^{14}$ -sucrose concentration was 4.0, while in oligodendrogliomas and astrocytomas the tumor/brain ratio of  $C^{14}$ -sucrose concentration was 13.2 and 20.2 resp. Sucrose content of brain tumors increased with elapsed time from injection of  $C^{14}$ -sucrose. Light microscopic autoradiography in 10 brain tumors revealed that radioactive sucrose remained predominantly extracellular, however, some sucrose grains were seen for the most part in the interstitial spaces between tumor cells. Inulin uptake by normal brain tissue was meager, and it was not possible to determine the localization of inulin in normal brain tissue.

- 0062 IN VITRO TRANSFORMATION OF RODENT CELLS BY K-REGION DERIVATIVES OF POLYCYCLIC HYDROCARBONS. (E.) Grover, P. L. (Chester Beatty Res. Inst., London, England), P. Sims, E. Huberman, H. Marquardt, T. Kuroki and C. Heidelberger. *Proc Nat Acad Sci USA* 68(6):1098-1101, 1971.

The K-region epoxides of benz(a)anthracene (BA), dibenz(a,h)anthracene (DBA), and 3-methylcholanthrene (MCA), the parent hydrocarbons, and the corresponding K-region dihydrodiols and phenols, into which such epoxides are converted by metabo-

lism were compared in both the hamster embryo and the mouse prostate cell systems to determine their relative ability to produce malignant transformation of cells in culture. The K-region epoxides and dihydrodiols derived from BA and DBA were found to be more active in the production of malignant transformation in hamster embryo cells than the hydrocarbons or the corresponding K-region phenols. The K-region epoxides derived from BA and from MCA were also active in transforming a clone of ventral prostate cells from a C3H strain mouse; the parent hydrocarbons were less effective than the epoxides in transforming these cells. The phenols were the most toxic compounds tested but did not transform cells.

- 0063 ULTRASTRUCTURAL OBSERVATIONS ON BRONCHIAL EPITHELIAL HYPERPLASIA AND SQUAMOUS METAPLASIA. (E.) Gould, V. E. (U. Washington Med. Sch., Seattle), R. Wenk and S. C. Sommers. *Cancer* 28(2):426-430, 1971.

Stainless steel pellets coated with 3.5-5.0 mg of 3-methylcholanthrene (MC) were implanted in the trachea of female rats; rats in another group were given pellets not coated with the carcinogen. Alterations produced in bronchial epithelium by carcinogen-treated and untreated pellets were observed under the electron microscope. By 4 wk after implantation of uncoated pellets, bronchi showed distinct basal and superficial layers. Basal cells showed moderately prominent rough endoplasmic reticulum and increased free ribosomes. Superficial cell layers showed invaginations in cell membranes and incomplete loss of cilia. The nuclear-cytoplasmic ratio was increased and large nuclei and double nucleoli were frequent. In bronchial epithelium of rats given MC-coated pellets the nuclear-cytoplasmic ratio was markedly increased and double nucleoli were again frequent. Cytoplasmic disintegration was often seen in superficial cells and superficial cells consistently lacked cilia. Abundant and complex cell interdigitations were seen by 8 wk after pellet implantation. Cell pleomorphism in intermediate cell layers was conspicuous. Keratohyalin granules were seen only in cells from rats given MC-coated pellets; this suggested that the carcinogen contact produced cells capable of keratin synthesis.

- 0064 HEPATIC LESIONS IN AGED RATS GIVEN CARBON TETRACHLORIDE AND 3-METHYLCHOLANTHRENE. (E.) Reuber, M. D. (Etiology Area., Natl. Cancer Inst., Bethesda, Md.) and L. F. Dove. *Path Microbiol* 37(2):122-131, 1971.

Male and female rats 8 and 76 wk of age were given s.c. injections of carbon tetrachloride ( $CCl_4$ ) in amounts of 1.3 ml/kg; some of the animals treated with  $CCl_4$  were given dietary doses of 3-methylcholanthrene (MC) in amounts of 0.033% added to food. Liver damage was assessed in both groups after 12 wk. Cirrhosis of the liver in 8-wk-old rats given only  $CCl_4$  was more severe in males than in females; all 12 male rats in the 8-wk-old age group developed cirrhosis and 7 developed



severe cirrhosis, whereas an equal number of female rats in this age group developed only 2 cases of severe cirrhosis. Younger rats were more liable to develop cirrhosis when given  $\text{CCl}_4$  than were older rats; among the 76-wk-old group none of the rats developed severe cirrhosis. MC treatment increased the incidence of severe cirrhosis in rats given  $\text{CCl}_4$ ; among 8-wk-old rats given both agents, 12 of 16 females developed severe cirrhosis and 12 of 15 males developed severe cirrhosis. Among 76-wk-old animals given both agents, 9 of 13 females and 11 of 14 males developed severe cirrhosis. Among other hepatic lesions seen in both groups of rats hyperplastic hepatic nodules were present more often in animals receiving both agents, especially among 76-wk-old rats. One female rat given both  $\text{CCl}_4$  and MC developed a transitional cell carcinoma of the urinary bladder.

0065 EXPERIMENTAL CEREBRAL GLIO-SARCOMAS IN MICE. (E.) Kroh, H. (Polish Acad. Sci., Warsaw, Poland). *Pol Med J* 10(1):218-226, 1971.

Cerebral gliosarcomas induced in strains  $\text{C}_3\text{H}$  and R III mice by methylcholanthrene were examined microscopically; of 18 tumors examined, 6 were tumors in which glial tissue predominated, 8 were tumors composed of approximately equal proportions of glial and mesodermal cells and 4 were tumors in which sarcoma tissue predominated. Tumors in the first group showed neoplastic proliferation of cells in the vascular walls; in these tumors, hypertrophy or hyperplasia of the elements of the vascular wall in specific tumors involved either single vessels or numbers of vessels. Most proliferating vascular wall vessels formed bands composed of large fusiform cells. In 3 of the 8 cases in the second group of tumors, neoplastic mesodermal tissue was related to the vascular system and formation of bands of fusiform cells on the vascular wall was seen. The 4 tumors in the third group were fibrosarcomas but were structurally different in several respects from conventional sarcomas. In none of the tumors was the degree of mesodermal proliferation correlated with a particular type of glioma.

0066 EFFECT OF POLYINOSINIC-POLYCYTIDYLIC ACID ON CHEMICALLY INDUCED TUMORIGENESIS BY METHYLCHOLANTHRENE IN MICE. (E.) Chandra, P. (Inst. Therapeutic Biochem., U. Frankfurt, Frankfurt, Germany), D. Gericke and A. Wacker. *Z Krebsforsch* 66(1):40-44, 1971.

Male and female albino mice of the AKR strain were given i.p. injections of 100  $\mu\text{g}$  of polyinosinic-polycytidylic acid (poly I:C) together with s.c. doses of 0.2 mg 3-methylcholanthrene (MC). In a group of mice not given poly I:C, 10 of 11 animals had developed tumors by 20 wk after MC treatment and 11 of 11 animals had developed tumors by 31 wk after treatment. In a group given poly I:C 24 hr prior to MC treatment, 5 of 9 animals had developed tumors by 20 wk and 6 of 9 by 31 wk. In a

group of mice given poly I:C 3 times per wk for 22 wk beginning 4 wk after MC treatment, 5 of 9 mice had developed tumors by the 15th wk after treatment and 8 of 9 had developed tumors by the 20 wk. Poly I:C administered beginning 8 wk after treatment did not decrease the incidence of tumors on treated mice; 10 of 10 mice so treated developed tumors. The mechanism by which poly I:C inhibited MC-induced tumor formation was studied. Mice given MC alone showed a 50% inhibition of the immune response to sheep red blood cells while mice given poly I:C following MC showed no reduction of the immune response to this antigen. In addition, pretreatments with poly I:C reversed the immunosuppressive reaction usually brought about by treatment with MC.

0067 TERATOGENIC EFFECTS INDUCED IN TAIL OF *Bufo arenarum* TADPOLES FOLLOWING TREATMENT WITH CARCINOGENS. (E.) De Lustig, E. S. (Fac. Med. Sci., U. Buenos Aires, Buenos Aires, Argentina) and E. L. Matos. *Experientia* 27(5):555-556, 1971.

Tadpoles of a species of toad (*Bufo arenarum*) were given s.c. implants of crystalline 3-methylcholanthrene (MC), 7,12-dimethylbenz(a)anthracene (DMBA) or benzo(a)pyrene (BP); agents were implanted in the middle of the tail. Tumors including papillomas developed in 90% of tadpoles treated with either of the 3 carcinogens; tumor cells invaded normal tail tissue. Among teratogenic effects observed after carcinogen treatment were an accessory tail fin developing in a tadpole given MC, complete accessory tail fins developing in tadpoles given DMBA, an accessory notochord developing in tadpoles given DMBA and accessory tail fins developing in tadpoles given BP. None of these effects were seen in tadpoles not treated with carcinogen.

0068 LEUKEMOGENESIS IN THE RAT: FURTHER OBSERVATIONS. (E.) Moloney, W. C. (Harvard Med. Sch., Boston, Mass.), M. Batata and V. King. *J Nat Cancer Inst* 46(6):1139-1144, 1971.

Leukemogenesis by X-irradiation, 3-methylcholanthrene (MCA) and splenectomy was observed in strain W/Fu and Fischer rats. In W/Fu rats given 150, 250 or 450 R of whole-body X-irradiation, the incidence of leukemia was not reduced compared to the expected incidence; 150 R increased the leukemia incidence in these rats by 8% over the expected incidence. When Fischer rats were given 250 R of irradiation, however, the incidence of leukemias was 4%, whereas the expected incidence was 24%. When W/Fu rats were given 40 mg MCA by stomach intubation, the observed incidence of leukemia was 42% and the expected incidence was 20%; when Fischer rats were given 80 mg MCA the observed and expected leukemia incidences approximately coincided (20 and 24%, resp.) No leukemias developed in 50 splenectomized Fischer rats. Cell-free material from plasma and spleen homogenates of leukemic rats was administered to syngeneic rats but failed to induce leukemia in the recipients.



- 0069 INVESTIGATION ON THE TUMOR PRODUCING EFFECT OF ISONICOTINIC ACID HYDRAZIDE IN ASW/Sn MICE AND MRC RATS. (E.) Toth, B. (U. Nebraska, Coll. Med., Omaha) and T. Toth. *Tumori* 56(6):315-324, 1970.

Isonicotinic acid hydrazide (INH) in a 0.1% solution was given in drinking water to strain ASW/Sn mice of both sexes and to rats of both sexes; mice and rats were 9- and 5-wk-old when INH feeding began, and treatments were continued for the life of the animals. The average daily intake of INH for mice was 2.9 mg for females and 2.8 mg for males, and the average daily intake of INH for rats was 20.6 mg for females and 30.2 mg for males. Sixty-eight percent of female mice given INH developed lung tumors (adenomas, adenocarcinomas or both) while 31% of male mice developed lung tumors. Thirty-four percent of untreated females developed lung tumors and 38% of untreated males developed lung tumors. Twelve percent of INH-treated female rats developed tumors of the mammary gland; 29% of untreated female rats developed mammary tumors. Tumors of the adenohypophysis were found in 1 treated female rat and in 48 untreated females (49% incidence). Eight percent of female rats and 4% of male rats developed malignant lymphoma following INH feeding; 11% of untreated female rats and 9% of untreated male rats developed malignant lymphoma.

- 0070 CARCINOGENICITY OF NITROSAMINE DERIVATIVES SUCH AS DMNA, DENA, MNU IN CHINESE HAMSTERS. (Rus.) Vasil'yeva, N. N. (Inst. Exp. Clin. Oncol. Acad. Med. Sci. Moscow, U.S.S.R.) and O. I. Sokova. *Vop Onkol* 17(4):58-63, 1971.

The carcinogenicity of 3 nitrosamine derivatives was investigated: dimethylnitrosamine (DMNA), diethylnitrosamine (DENA) and methylnitrosourea (MNU). One hundred and fifty Chinese hamsters, 2-3 months-old, were treated s.c. with 33 mg/kg of DMNA, DENA, or MNU for 14-20 wk. Tumors appeared 3.5 months after the beginning of MNU treatment and after 5.0-5.5 months with each of the other 2 compounds. The highest incidence of tumors (62.5%) was observed in the MNU-treated group and the lowest (18%) appeared in the DMNA-treated group. MNU induced malignant skin tumors in 16 cases and leukemia in 14 cases. A number of benign tumors were formed as well and the group in general was characterized by multiple tumor formation as well as a low incidence of lung and liver neoplasia. Precancerous alterations such as adenomatous hyperplasia of the pulmonary, hepatic and endometrial epithelium were observed in 4 MNU-treated hamsters. DENA induced 17 tumors in 13 of 50 hamsters; its main target organs appeared to be the lung and the liver.

- 0071 FORMATION OF N-NITROSOPIPERIDINE FROM PIPERIDINE AND SODIUM NITRITE IN THE STOMACH AND THE ISOLATED INTESTINAL LOOP OF THE RAT. (E.) Alam, B. S. (Children's Cancer Res. Fdn., Inc., Boston, Mass.), I. B. Saporoschetz and S. S. Epstein. *Nature* 232(5306):116-118, 1971.

Portions of the small intestine of male rats were exposed surgically and loops were produced

by tying off segments of the intestine with ligatures; in other rats the stomach was isolated between ligatures. Piperidine hydrochloride and sodium nitrite were introduced into intestine or stomach through tubes and the *in vivo* formation of nitrosopiperidine was observed. In the small intestine piperidine hydrochloride was administered in amounts of 125, 625 or 1,250 mg and the amount of sodium nitrite was held constant at 25 mg. In the small intestine, the yield of nitrosopiperidine depended on the piperidine concentration and ranged from 0-159 µg. In the stomach, piperidine hydrochloride was administered in amounts of 312.5, 500 or 625 mg and sodium nitrite was administered in amounts of 10, 12.5 or 25 mg. The yield of nitrosopiperidine in the stomach ranged from 11-40 µg. In the *in vitro* experiments, intestinal washings and gastric juices of rats treated with piperidine hydrochloride and sodium nitrite were incubated aerobically and the yield of nitrosopiperidine in the incubation mixtures was determined. Nitrosopiperidine was produced by gastric juice incubation mixtures in amounts ranging from 327-785 µg; nitrosopiperidine was not produced *in vitro* from its precursors in small intestinal washings.

- 0072 A FOCUS OF RUMENAL CANCER IN KENYAN CATTLE. (E.) Plowright, W. (East Africa Veterinary Res. Org., Kabete, Kenya), C. A. Linsell and F. G. Peers. *Brit J Cancer* 25(1):72-80, 1971.

Post-mortem examinations were performed on 20 domestic cattle from herds maintained in the Nasampolai valley of Kenya Masailand; the cattle had died of a disease well known in the area which was marked by symptoms including rumenal tympany, abdominal pain and partial anorexia. Squamous cell carcinoma of the rumen was present in all cases examined, and in each case the anterior wall of the dorsal sac of the rumen was affected. Tumors were of the ulcerative and/or fungating type and appeared to be multicentric in origin. Wide invasion of the rumenal wall was common. Metastases were found in 4 animals and involved the atrial and posterior mediastinal lymph nodes. Rumenal cancer was thought to account for an annual mortality of 5% in these cattle. The practice of grazing herds in cleared forest areas was believed to be etiologically related to the incidence of rumenal cancer. Specifically, it was suggested that the ingestion of nitroso-compounds by forest-grazing cattle may have caused the development of rumenal carcinoma in affected animals.

- 0073 MUTAGENICITY IN YEAST OF NITROQUINOLINES AND RELATED COMPOUNDS. (E.) Epstein, S. S. (Children's Cancer Res. Fdn., Inc., Boston, Mass.) and J. A. St. Pierre. *Toxic Appl Pharmacol* 15(2):451-460, 1969.

Cultures of *Saccharomyces cerevisiae* were exposed to 14 quinoline compounds to determine which quinolines were mutagenic for the bacteria; mutagenicity was tested by observing the development of respiratory

deficient mutant bacteria. The mean spontaneous mutation rate for *S. cerevisiae* colonies not exposed to quinolines was 3.5%. Six quinolines were strongly mutagenic; the concentrations of these quinolines which doubled the spontaneous mutation rate ranged from 0.06-0.5 µg/ml. In order of their mutagenic potency, the 6 strongly mutagenic quinolines were: 4-nitroquinoline 1-oxide, 8-methyl-4-nitroquinoline 1-oxide, 7-methyl-4-nitroquinoline 1-oxide, 2-methyl-4-nitroquinoline 1-oxide, 6-methyl-4-nitroquinoline 1-oxide and 7-chloro-4-nitroquinoline 1-oxide. Two quinolines were less strongly mutagenic (mutagenic potencies of 0.11 and 0.04): 4-nitroquinoline and 4-hydroxyaminoquinoline 1-oxide HCl. Six quinolines were not mutagenic. The 8 mutagenic quinolines were mutagenic at concentrations which were growth-inhibiting. All the mutagenic quinolines were carcinogenic; none of the 6 non-carcinogenic quinolines studied was mutagenic.

0074 EFFECT OF SMOKING DURING PREGNANCY ON THE RISK OF CANCER IN CHILDREN. Neutel, C. I. Dept. Comm. Med. U. Western Ontario, London, Canada) and C. Buck. *J Nat Cancer Inst* 47(1):59-63, 1971.

Smoking histories were ascertained for mothers of 9,302 infants and the incidence of cancer in these infants was determined to establish whether prenatal smoking is related to cancer in offspring. Among children of mothers who smoked 1 package of cigarettes or less/day (including nonsmokers) the incidence of cancer was 13.8 cases/100,000 child yr, while among children of mothers who smoked 1 package of cigarettes or more/day the cancer incidence was 10.7 cases/100,000 child yr. This difference was found not to be statistically significant. The relative risk of cancer development for children of light and heavy smokers combined, compared to the risk for nonsmokers was 1.3. It was concluded that, while *in utero* exposure to tobacco smoke probably does not have a carcinogenic effect on the fetus, a lesser general effect or an effect confined to a single tissue may be produced.

0075 CIGARETTE SMOKE CARCINOGENESIS: IMPORTANCE OF TUMOR PROMOTERS. (E.) Van Duuren, B. L. Inst. Environ. Med., New York U., N.Y.), A. Sivak, J. Katz and S. Melchionne. *J Nat Cancer Inst* 47(1): 235-240, 1971.

Female strain ICR/Ha Swiss mice were given a single topical application of 50 µg 7,12-dimethylbenz(a)anthracene (DMBA) as a tumor initiator followed after 14 days by topical applications of 40 mg tobacco smoke condensate (5 applications/wk); another group of mice was given DMBA followed by benzo(a)pyrene. Of 60 mice given DMBA and tobacco smoke condensate, 16 had developed tumors by 573 days after DMBA treatment; 14 of these mice had developed carcinomas. Eighteen of 60 mice given tobacco smoke condensate without DMBA developed tumors by day 573 (4 carcinomas) and 8 of 60 mice given DMBA followed

by acetone developed tumors (no carcinomas). Of 30 mice given DMBA and benzo(a)pyrene 21 had developed tumors by day 462 (11 carcinomas) and of 20 mice given benzo(a)pyrene and no DMBA 8 developed tumors (1 carcinoma). Tumors, other than "carcinomas", which developed on mice were diagnosed as papillomas.

0076 NUCLEOPHILIC ATTACK ON 4-AMINOMETHYLENE-OXAZOL-5(4H)-ONES, A RATIONALISATION OF PENICILLIN CARCINOGENICITY. (E.) Longridge, J. L. (Imperial Chem. Industries, Ltd., Macclesfield, Cheshire, England) and D. Timms. *J Chem Soc (Org)* 5:848-851, 1971.

The chemistry of penicillenic acid and other structurally similar oxazolone systems was investigated in the course of a chemical interpretation of penicillin carcinogenicity. When hydrolyzed at pH7 penicillenic acid gave penicilloic acid, and its oxazolone ring was readily attacked by nucleophiles at the carbonyl group to yield acylated products. The intramolecular nucleophilic attack was found to be prevented in concentrated (1.0 M) alkaline solution (when hydroxymethylene-oxazolone was formed) or by oxidation of penicillenic acid to its disulphide. The binding site of thiols with penicillenic acid seemed to be determined by the oxidation state of the thiol on the penicillamine group and binding of nucleophiles seemed to occur *via* alkylation when the oxidized form is present. Penicillin carcinogenicity was rationalized as an alkylation reaction thus conforming to the pattern established by other chemical carcinogens.

0077 CANCER AMONG MEN ON CHOLESTEROL-LOWERING DIETS: EXPERIENCE FROM FIVE CLINICAL TRIALS. (E.) Ederer, F. (Natl. Heart Lung Inst., Natl. Inst. Hlth., Bethesda, Md.), P. Leren, O. Turpeinen and I. D. Frantz, Jr. *Lancet* 2(7717): 203-206, 1971.

Studies on the incidence of cancer and on cancer mortality among men on an unsaturated fat, cholesterol-lowering diet were carried out in Oslo, London, Helsinki and Faribault, Minnesota. Results were compared with results obtained from a similar study carried out in Los Angeles. In the latter study an excessive cancer incidence and mortality was found among men on the cholesterol-lowering diet; the relative risk of developing cancer for men was 1.28. Studies performed in London, Helsinki and Faribault failed to confirm these results; the relative risk for cancer development among cholesterol-lowering diet patients in London, Helsinki and Faribault were 0.24, 0.78 and 0.34 resp. Results from Oslo were closer to results from Los Angeles; in Oslo the relative risk for cancer development among men on the cholesterol-lowering diet was 1.43. The close approximation of all the relative risk indices to unity suggested that a cholesterol-lowering diet does not present a clear danger of cancer development.



- 0078 COFFEE DRINKING AND CANCER OF THE LOWER URINARY TRACT. (E.) Cole, P. (Harvard Sch. Pub. Hlth., Boston, Mass.). *Lancet* 1(7713): 1335-1337, 1971.

Interviews were conducted with 468 patients in the Boston area who had cancer of the renal pelvis, ureter, bladder or urethra; results confirmed the association of bladder cancer risk with cigarette smoking. In addition, an association was found between coffee drinking and bladder cancer risk. When data were controlled for age, cigarette smoking and occupation it was found that the numbers of observed and expected cases of bladder cancer among drinkers of less than 1 cup of coffee per day were 29 vs. 41.3, resp., among males and 9 vs. 22.9, resp., among females. Among drinkers of more than 4 cups of coffee per day, the numbers of observed and expected bladder cancer cases were 84 vs. 71.8, resp., among males and 22 vs. 19.4, resp., among females. Data yielded relative risks of developing bladder cancer of 1.24 for male coffee drinkers and 2.58 for female coffee drinkers; the risk of developing bladder cancer for persons who drank no coffee was 1.00. The association of bladder cancer and coffee drinking was stronger for women than for men; among male coffee drinkers the cancer risk increased with age.

- 0079 CARCINOGENICITY OF EXTRACTS OF SELECTED PLANTS FROM CURACAO AFTER ORAL AND SUBCUTANEOUS ADMINISTRATION TO RODENTS. (E.) O'Gara, R. W. (Nat'l. Cancer Inst., Bethesda, Md.), C. Lee, and J. F. Morton. *J Nat Cancer Inst* 46(6):1131-1137, 1971.

Decoctions were prepared from the leaves of herbs and other plants in use as medicines among esophageal cancer patients in Curacao; plant extracts were administered orally or by s.c. or i.m. injection to Swiss mice or rats. Plants used in the tests included *Krameria iwinia*, *Citrus aurantium* (Iaraha), *Annona muricata* (sorsaka), *Heliotropium ternatum* (sali) and *Gliricidia sepium* (raton). All of 15 rats given s.c. injections of 1 ml undiluted *K. iwinia* extract once a week for 14 months developed fibrosarcomas at the site of injection. Sorsaka, sali, Iaraha and raton each produced s.c. sarcomas in 1 or 2 of 15 rats when administered by s.c. injection. Tumors induced by extracts were fibrosarcomas. Plant extracts administered orally induced no tumors. No gross or microscopic changes attributable to the ingested plant materials were seen in the esophagus of either mice or rats.

- 0080 ACUTE TOXICITY OF AFLATOXINS B<sub>1</sub> AND G<sub>1</sub> IN THE RAINBOW TROUT (*Salmo gairdneri*). Bauer, D. H. (Dept. Food Sci. and Tech., Oregon State U., Corvallis), D. J. Lee and R. O. Sinnhuber. *Toxic Appl Pharmacol* 15(2):415-419, 1971.

- 0081 THE DEVELOPMENT OF GLASS-FIBRE BODIES IN THE LUNGS OF GUINEA-PIGS. (E.) Botham, S. K. (Dept. Chem., U. Reading, Berkshire, England) and P. F. Holt. *J Path* 103(3):149-156, 1971.

- 0082 APLASTIC ANAEMIA, ACUTE MYELOBLASTIC LEUKAEMIA, AND OXYMETHOLONE. (E.)

Delamore, I. W. (Manchester Royal Infirm., Manchester, England) and C. G. Geary. *Brit Med J* 2 (5764):743-745, 1971.

- 0083 VAGINAL CANCER AFTER MATERNAL TREATMENT WITH SYNTHETIC ESTROGENS. (E.) Greenwald, P. (New York State Dept. Hlth., Albany), J. J. Barlow, P. C. Nasca and W. S. Burnett. *New Eng J Med* 285(7):390-392, 1971.

- 0084 REDUCED CARCINOGENIC EFFECTS OF AFLATOXIN IN RATS GIVEN PHENOBARBITONE. (E.) McLean, A. E. M. (U. Coll. Hosp. Med. Sch., London, England) and A. Marshall. *Brit J Exp Path* 52(3): 322-329, 1971.

- 0085 MYCOLOGICAL AND SEROLOGICAL STUDIES ON *Aspergillus flavus* ISOLATED FROM PARANASAL ASPERGILLOMA IN SUDAN. (E.) Mahgoub, E. S. (Fac. Med., U. Khartoum, Khartoum, Sudan). *J Trop Med Hyg* 74(7):162-165, 1971.

- 0086 SPECIFICATIONS FOR CUTTING OILS WITH SPECIAL REFERENCE TO CARCINOGENICITY. (E.) Catchpole, W. M. (British Petroleum Co., Ltd., Sunbury-on-Thames, Middlesex, England), E. Macmillan and H. Powell. *Ann Occup Hyg* 14:171-179, 1971.

- 0087 TRANSPLANTABLE MALIGNANT CHOLANGIOCARCINOMA FROM HAMSTER LIVER. (E.) Glaser, O. G. (Dept. Nutrition and Food Sci., Massachusetts Inst. Technology, Cambridge), P. M. Newberne, J. Gabliks and L. Friedman. *Arch Environ Health* 23(2): 137-141, 1971.

- 0088 PROMOTION IN THE MORPHOGENESIS OF CHEMICALLY INDUCIBLE SKIN TUMOURS: A HISTOLOGICAL AND HISTOCHEMICAL STUDY. (E.) Stenbäck, F. (Dept. Path., U. Oulu, Oulu, Finland). *Acta Path Microbiol Scand* 208:1-105, 1969.

- 0089 NASAL CANCER IN FURNITURE-MAKERS IN DENMARK. (E.) Mosbech, J. (Copenhagen Cty. Hosp., Copenhagen, Denmark) and E. D. Acheson. *Danish Med Bull* 18(2):34-35, 1971.

- 0090 OXIDATION OF SEVERAL AROMATIC HYDROCARBONS USING DIMETHYL SULFOXIDE EXPOSED TO THE ATMOSPHERE. (E.) Haga, J. J. (Dept. Chem., North Texas State U., Denton), B. R. Russell and J. F. Chapel. *Biochem Biophys Res Commun* 44(3):521-525, 1971.

0091 CARCINOMA OF THE MAXILLARY ANTRUM AND ITS RELATIONSHIP TO TRACE METAL CONTENT OF SNUFF. (E.) Baumslag, N. (U. Cincinnati Coll. Med., Cincinnati, O.), P. Keen and H. G. Petering. *Arch Environ Health* 23(1):1-5, 1971.

0092 CARCINOGENIC NITROGEN COMPOUNDS: LXXI. ACRIDINES FROM 5-AMINOBENZO (b) SELENO-PHEN. (E.) Buu-Hoi, N. P. (Inst. Chem. Nat. Substances, C.N.R.S., Gif-sur-Yvette, France), M. Dufour, P. Jaquignon, M. Renson, G. Marechal and A. Rumet. *J Chem Soc* 12(7):2308-2310, 1971.

0093 TRANSPLACENTAL CARCINOGENESIS BY STIL-BESTEROL. (E.) Folkman, J. (no affil). *New Eng J Med* 285 (7):404-405, 1971.

0094 PREPARATION OF LABELED AFLATOXINS WITH HIGH SPECIFIC ACTIVITIES. (E.) Hsieh, D. P. H. (Dept. Environ. Toxicol., U. California, Davis) and R. I. Mateles. *Appl Microbiol* 22(1):79-83, 1971.

0095 EXPERIMENTAL CERVICAL DYSPLASIA IN THE RHESUS MONKEY: II. (E.) Kaminetzky, H. A. (U. Illinois Med. Ctr., Chicago, Ill.) *Obstet Gynec* 38(2):232-238, 1971.

0096 ULTRASTRUCTURE OF HUMAN ORAL MUCOSA AFTER PROLONGED EXPOSURE TO TOBACCO. (E.) Luthra, U. K. (Indian Council Med. Res., New Delhi), D. A. Woods, P. N. Wahi and M. Gupta. *Indian J Med Res* 59(1):157-162, 1971.

0097 FATE OF ARENES INCORPORATED WITH AIRBORNE SOOT: EFFECT OF IRRADIATION. (E.) Tebbens, B. D. (Sch. Pub. Hlth., U. California, Berkeley), M. Mukai and J. F. Thomas. *Amer Industr Hyg Ass J* 32(6):365-372, 1971.

0098 MUCOSAL CHANGES AND CANCER IN INTRA-ORAL SMOKING. (E.) Morrow, R. C. (Cartagena, Colombia) and G. Suarez. *Laryngoscope* 81(7):1020-1028, 1971.

See also:

- \* (Rev): 0004, 0022, 0026, 0029, 0032
- \* (Viral): 0140
- \* (Immun): 0163
- \* (Epid-Biom): 0200



- 0099 IRRADIATION-INDUCED LESIONS IN GERM-FREE RATS. (E.) Pollard, M. (Lobund Lab., U. Notre Dame, Notre Dame, Ind.) and N. Sharon. *J Nat Cancer Inst* 47(1):229-237, 1971.

Germ-free and conventional rats were exposed to a total of 800 r of whole-body X-irradiation and the incidence of tumors of various types was observed. Ten of 12 irradiated germ-free Wistar strain rats developed a variety of benign and adenomatous lesions including adenofibroma of the breast, monocytic leukemia, degeneration of the pancreas, islet cell tumors and hepatomas. Breast tumors were most common in this group. Ten of 12 irradiated germ-free Fischer strain rats developed adenocarcinoma of the breast (6 cases), adenoma of the adrenal medulla, pancreatic adenomas and islet cell tumors. In irradiated germ-free Fischer and Wistar strain rats tumors were found to have developed by 15 months of age. Conventional unirradiated Wistar rats developed a more extensive array of tumors than did germ-free irradiated rats; 17 of 20 rats in this group developed tumors. These tumors included adrenal medullary tumors, adenoma of the adrenal cortex, metastasizing adenocarcinoma of the breast, monocytic leukemia and adenofibroma of the breast. Lung infections were also common in the conventional rats.

- 0100 BLASTOGENIC ACTION OF IONIZING RADIATION IN DOGS. (Rus.) Shikhodyrov, V. V. (Moscow, U.S.S.R.), G. A. Lebedeva, B. I. Lebedev and N. K. Yevseyeva. *Vop Onkol* 17(5):55-60, 1971.

Thirty-three of 56 dogs developed tumors after s.c. administration of  $^{210}\text{Po}$  (2.5  $\mu\text{C/kg}$ ) or whole-body exposure to  $\gamma$ -rays (172-1060 roentgen equivalents). The highest incidence of tumors was observed 6-9 yr after exposure to either of these radiations.  $^{210}\text{Po}$  induced a 30% incidence of tumors oriented mainly towards the storage or excretion organs such as the liver, kidney, bladder or exocrine pancreas.  $\gamma$ -radiation induced tumors of subcutaneous tissues. Alterations preceding tumor development following  $^{210}\text{Po}$  administration consisted in slow dystrophic processes leading to the formation of hyperplastic foci within the target organs. The development of multiple tumors with low metastatic potentialities seemed to constitute a characteristic feature following irradiation.

- 0101 TRANSPLANTATION OF RADIATION-INDUCED CANINE MYELOMONOCYTIC LEUKAEMIA. (E.) Shifrine, M. (Radiol. Lab., U. California, Davis), M. S. Bulgin, N. E. Dollarhide, H. G. Wolf, N. J. Taylor, F. D. Wilson, D. L. Dungworth and Y-C. Zee. *Nature* 232(5310):405-406, 1971.

A female beagle, fed  $^{90}\text{Sr}$  daily from birth to a final accumulation of 5,000 rads of  $\beta$ -irradiation in bone marrow developed myelomonocytic leukemia by 5 yr of age. White blood cell numbers were increased and there was an excessive rise in the percentage of granulocytes relative to other cell

types in the bone marrow. The dog also showed invasion of bone marrow, liver, spleen and lymph nodes. Bone marrow cell preparations from the original dog with myelomonocytic leukemia were injected into fetal beagles; the number of viable cells injected varied from  $1 \times 10^7$  to  $2 \times 10^8$  cells/ml. Inoculation of fetal dogs was performed at 46-53 days of gestation. Lesions produced in fetally inoculated beagles (by 8-71 days after birth) resembled lesions in the original donor beagle; in all recipients of leukemic bone marrow, large retroperitoneal masses of chloromatous tumor tissue appeared in the sublumbar region. Serum lysozyme concentrations were high in the primary donor of leukemic cells and were also high in all leukemic recipients of tumor cells; lysozyme concentrations, however, were normal in all non-leukemic beagles.

- 0102 THE ROLE OF INSOLATION IN SKIN CARCINOGENESIS. (Rus.) Kronrod, B. A. (Moscow Med. Stomatol. Inst., U.S.S.R.) and L. R. Rubin. *Vestn Derm Vener* 45(2):50-55, 1971.

Ultraviolet (UV) radiation as an exogenous factor inducing skin neoplasia is discussed and illustrated by clinical data from 6900 skin tumor patients. The incidence of basal cell carcinoma was 18 times higher on exposed than on garment-covered skin; squamous cell carcinoma, keratoma, and papilloma develop more often in exposed than in garment-covered portions of the skin by factors of 7, 4 and 2 respectively. Bowen's disease and skin melanoma constitute exceptions in that they develop on covered portions of the skin. The hair-covered portion of the scalp is 6-7 times less affected by squamous cell carcinoma or basal cell carcinoma than the facial region. Skin sensitivity to UV radiation, however, varies according to color, region, age and condition. The climatic factor as related to epidemiology of skin neoplasia throughout the U.S.S.R. is reviewed.

- 0103 TOTAL BODY IRRADIATION AND HUMAN CHROMOSOMES: II. CYTOGENETIC STUDIES OF THE CULTURED BONE MARROW CELLS SEVEN YEARS AFTER TOTAL BODY IRRADIATION. (E.) Goh, K.-O., (Med. Div., Oak Ridge Associated Universities, Oak Ridge, Tenn.) *Amer J Med Sci* 262(1):43-49, 1971.

Cytogenetic studies were carried out on bone marrow cells taken from 6 male subjects who, 7 yr prior to the date of examination, had been accidentally exposed to total body irradiation with fast neutrons and gamma-rays; the radiation exposure range among the subjects was 22.8-365 rads. None of the subjects developed cancer or hematologic disease. A total of 725 metaphases from the 6 subjects were examined. The modal chromosome number was 46 (seen in 88% of metaphases); 20 dicentric chromosomes were seen in hypodiploid metaphases. Of the metaphases examined, 14.8% were abnormal; chromosomal abnormalities included fragments (present in 9.8% of metaphases), dicentrics (present in 2.8% of metaphases), translocations (present in 2.1% of metaphases), rings



(present in 0.3% of metaphases) and smaller G chromosomes (present in 2.3% of metaphases). Although the frequency of chromosomal breaks and abnormalities was higher in bone marrow cells from irradiated subjects than in bone marrow cells of normals, frequencies of abnormalities in the bone marrow cells of irradiated subjects were similar to frequencies of abnormalities in peripheral leukocytes from the irradiated subjects. Fewer mitoses and fewer abnormalities were seen in bone marrow cells not exposed to phytohemagglutinin (PHA) than in bone marrow cells stimulated with PHA; no dicentric and only 1 ring were seen in cultures of bone marrow cells not exposed to PHA. Marker chromosomes, including a smaller G chromosome and a large acrocentric chromosome were seen in cultures of cells not exposed to PHA; these markers are found in patients with leukemia or cancer.

0104 CARCINOMA OF THE THYROID FOLLOWING IONIZING RADIATION FOR HODGKIN'S DISEASE. (E.) Meyer, O. O. (U. Hosp., U. Wisconsin, Madison). *Wisconsin Med J* 70 (5):129-133, 1971.

0105 STRONTIUM-90 IN THE BONE OF DIFFERENT SOUTH AFRICAN POPULATION GROUPS. (E.) Van As, D. (Atomic Energy Board, Pelindaba, South Africa) and H. O. Fourie. *S Afr Med J* 45(25):694-696, 1971.

0106 REGENERATION OF INTESTINAL MUCOSA AFTER IRRADIATION. (E). Withers, H. R. (U. Texas M. D. Anderson Hosp., Houston). *Cancer* 28(1):75-81, 1971.

0107 THE QUESTION OF SAFE RADIATION THRESHOLDS FOR ALPHA EMITTING BONE SEEKERS IN MAN. (E). Gofman, J. W. (Lawrence Radiation Lab., U. California, Livermore) and A. R. Tamplin. *Health Physics* 21(1):47-51, 1971.

0108 THOROTRAST QUANTITIES AND WHOLE-BODY COUNTS. (E). Hemphill, F. M. (Environ. Hlth. Service, Rockville, Md.) and R. D. Hesselgren. *Health Physics* 21(1):85-89, 1971.

0109 EFFECTS OF THERAPEUTIC PROTON DOSES ON HEALTHY ORGANS IN THE NECK, CHEST AND UPPER ABDOMEN OF THE RABBIT. (E.) Danielsson, M. (Gustaf Werner Inst., U. Uppsala, Uppsala, Sweden), B. Engfeldt, B. Larsson, C. Naeslund and J. Naeslund. *Acta Radiol* 10(2):215-224, 1971.

See also:

- \* (Rev): 0022, 0027, 0031
- \* (Chem): 0038, 0068, 0081
- \* (Viral): 0119, 0136

- 0110 PRODUCTION OF ANTIGENS ASSOCIATED WITH EPSTEIN-BARR VIRUS IN EXPERIMENTALLY INFECTED LYMPHOBLASTOID CELL LINES. (E.) Pearson, G. R. (Sch. Med., U. Pennsylvania, Philadelphia), G. Henle and W. Henle. *J Nat Cancer Inst* 46(6): 1243-1250, 1971.

Epstein-Barr virus (EBV) was used to infect cells from each of 3 lymphoblastoid cell lines: the RPMI-6410 line, derived from leukocytes of a patient with myelogenous leukemia, the Raji line, a line of Burkitt's tumor cells, and the SKL-1 line, derived from leukocytes of a patient with myelomonocytic leukemia. On EBV infection, the 6410 line produced early antigen (9-10% of cells antigen-positive) but did not produce membrane antigen or viral capsid antigen. SKL-1 cells produced all 3 types of antigen; by day 2 postinfection, 6-7% of SKL-1 cells were positive for capsid antigen, 14-15% were positive for early antigen, and 32% were positive for membrane antigen. Raji cells also produced all 3 types of antigen; by day 2 postinfection, 1-2% of Raji cells were positive for capsid antigen, 28-29% were positive for early antigen and 15% were positive for membrane antigen. In EBV-infected SKL-1 and Raji cells early antigen synthesis was detectable by 6-8 hr postinfection whereas membrane antigen and capsid antigen synthesis were not detectable until about 12 hr postinfection. When virus-infected cells were absorbed with membrane antigen-positive cells the activity of neutralizing antibodies was reduced; this effect was not produced by absorbing infected cells with membrane antigen-negative lymphoblastoid cells.

- 0111 CYTOCHEMICAL AND IMMUNOFLOUORESCENCE STUDY OF AN ONCOGENIC AVIAN ADENOVIRUS (CELO) IN MAMMALIAN CELL CULTURES. (E.) Miller, L. T. (Animal Path. Dept., U. Rhode Island, Kingston) and V. J. Yates. *Infect Immun* 4(2):173-175, 1971.

Chicken embryo lethal orphan virus (CELO) was prepared from chick embryo kidney cells and inoculated into cultures of African green monkey kidney cells (GMK) (50-100 PFU/cell) or into cultures of adult hamster kidney cells (100 PFU/cell). Virus replication was limited in both mammalian cell cultures; in GMK cells no replication of CELO virus was seen at 30 hr postinoculation, while in chick embryo kidney cells the virus had replicated to the 5.5 log ELD<sub>50</sub> (i.e., median embryo lethal dose) level by 30 hr. In mixed GMK and chick embryo kidney cell cultures the virus replicated at a level similar to its level of replication in chick embryo kidney cell cultures. CELO virus apparently did not replicate at all in hamster kidney cell cultures. Neoantigen was produced in hamster kidney cells after 8 days postinoculation; GMK cells inoculated with CELO virus produced neoantigen by 48 hr postinoculation. It was concluded that CELO virus infection of GMK cells and hamster kidney cells, where it occurred, was abortive.

- 0112 TUMOR INDUCTION BY MURINE LEUKEMIA/SARCOMA VIRUSES: MORPHOLOGICAL AND IMMUNOLOGICAL STUDIES. (E.) Chieco-Bianchi, L. (Div. Exp. Oncol., U. Padua, Italy), N. Pennelli, D. Collavo and G. Tridente. *Advances Exp Med Biol* 12:555-565, 1971.

BALB/c strain mice, aged 1-2 or 4-6 wk-old were given i.m. injections of Moloney murine sarcoma virus (MSV (M)) in various dilutions and the incidence of ensuing sarcomas was observed. Younger mice showed a higher tumor incidence than older mice; the tumor incidence among 1-2-wk-old mice given a 10<sup>-2</sup> dilution of MSV (M) was 97.5% while the incidence of tumors among 4-6-wk-old mice given a 10<sup>-2</sup> virus dilution was 48%. The mean latent period of tumor appearance was longer in older mice than in younger mice. More older mice developed regressing tumors than did younger mice. Mice given virus during the first 2 wk of life showed no marked splenic enlargement while mice given virus at 4-6-wk-old showed splenic enlargement. When mice were treated with pre-immunized spleen cells prior to injection of MSV(M) the incidence of tumors was high but the period between injection of virus and death of the mouse was prolonged in comparison to mice given only virus. When mice were infected at birth with Graffi virus and given MSV(M) thereafter, the tumor incidence was found to be high; mice infected with Graffi virus and given a later injection of MSV(M) developed tumors in 34 of 35 cases. Of 20 mice infected at birth with Passage A Gross leukemia virus and given a later MSV(M) injection, only 2 developed tumors.

- 0113 THE EFFECTS OF PROTAMINE ON A MURINE LEUKEMIA VIRUS. (E.) Bates, H. A. (Swedish and St. Barnabas Hosps. Res. Fdn., Minneapolis, Minn.), D. S. Amatzio, L. Hay, D. J. Conklin and F. B. Becker. *Brit J Cancer* 25(1):130-134, 1971.

Mice of the BALB/c/Tex strain were inoculated with Rauscher leukemia virus at 1 day old and when hepatosplenomegaly appeared and mice began to die, protamine was injected i.p. thrice weekly for 6 wk in concentrations of 0.2 mg/10 g body wt, 0.4 mg/10 g, 0.6 mg/10 g and 1.0 mg/10 g. Leukemic mice not given protamine died in 50 of 50 cases with a mean death time of 40 days. Leukemic mice given 0.2 mg protamine/10 g body wt died in 40 of 40 cases with a mean death time of 50 days and leukemic mice given 0.6 mg protamine/10 g died in 28 of 30 cases with a mean death time of 78 days. In the latter group hepatosplenomegaly started to regress 4-6 wk after inoculation of the virus. Protamine was not toxic for nonleukemic mice; none of 25 healthy mice given protamine died. In a related experiment, Rauscher virus and protamine were incubated *in vitro* and inoculated into mice. Virus incubated with protamine showed reduced infectivity compared to virus not incubated with protamine.



0114 VIRUS INDUCED MALIGNANT LYMPHOMA IN MICE DEPENDENT ON A RES "CONDITIONED" BY CHRONIC PARASITIC INFECTION (*P. berghei*). (E.) Jerusalem, C. (Lab. Cyto-Histology, U. Nijmegen, Netherlands), P. Jap and W. Eling. *Advances Exp Med* 15:391-399, 1971.

Swiss mice were infected with malarial parasite, *Plasmodium berghei*, and the incidence of spontaneously developing solid lymphomas was observed; mice were given light, moderate or severe parasite infections. Lymphomas developed in 6.25% of mice not infected with *P. berghei* and in 10.0% of lightly infected mice; 17.5% of mice given moderate malarial infection, and 30.0% of mice given severe malarial infection, developed lymphomas. Aleukemic lymphomas developed earlier in moderately and severely infected mice than in mice with less extensive malarial infections. There were fewer carcinomas in those mice which were given severe or moderate malarial infections than in mice with no infection or with slight infection. Virus particles, usually of the A<sub>1</sub> and C types, were seen more often in mice with severe malarial infections than in mice in other groups. In a related experiment, infected and uninfected mice were given cell-free tumor extracts from aleukemic lymphomas. Three months after transplantation, 13.9% of mice with malarial infections developed aleukemic lymphomas and 2.8% of uninfected mice developed aleukemic lymphomas. No aleukemic lymphomas developed in infected mice not inoculated with cell-free extract.

0115 GRAFFI VIRUS-INDUCED LEUKEMIA IN MICE: I. MORPHOLOGICAL INVESTIGATIONS. (Pol.) Papla, B. (Acad. Med., Krakow, Poland), A. Hiezaitrowski. *Pat Pol* 22(2):259-270, 1971.

Morphological alterations following s.c. inoculation with 0.1-0.2ml of a cell-free preparation from Graffi virus-induced murine leukemia were investigated in 50 white mice. No changes were observed during the early period following inoculation. The spleen revealed lymphatic follicles with obliterated boundaries 20 days after inoculation. A narrowing of the cortical portion and widening of the medullar portion were then observed in the thymus. Leukemic infiltrates were seen simultaneously in the spleen (around the trabeculae) and in the thymus 58 days after inoculation. Leukemic cell infiltration of the entire spleen and thymus parenchyma as well as the liver and kidney was observed upon development of the entire leukemic syndrome.

0116 GRAFFI VIRUS-INDUCED LEUKEMIA IN MICE: II. HISTOCHEMICAL INVESTIGATIONS OF ACID AND ALKALINE PHOSPHATASES AND NONSPECIFIC ESTERASES IN DIFFERENT ORGANS. (Pol.) Papla, B. (Acad. Med., Krakow, Poland), A. Niezabitowski, M. Dubiel-Bigaj. *Pat Pol* 22(2):271-285, 1971

The liver of Graffi virus-treated mice revealed a marked enlargement and an enhanced proliferation of Kupffer cells with increased acid phosphatase and non-specific esterase activities in their cytoplasm 5 days after the infection. A distinct increase in alkaline phosphatase within the lymphatic follicles of the spleen could be observed 1-10 days following inoculation. These lymphatic follicles were found to be enlarged and to contain large proliferating cells with positive reactions for acid phosphatase and non-specific esterase 20 days after infection. The cells of the leukemic infiltrates elicited weak reactions for alkaline phosphatase and some manifested positive reactions for acid phosphatase and non-specific esterase.

0117 IN VITRO PRODUCTION OF MURINE LEUKEMIA VIRUS BY CELLS DIFFERING IN A SINGLE ALLELE. (E.) Hackett, A. J. (Sch. Pub. Hlth., U. California, Berkeley), J. S. Manning and R. B. Owens. *J Nat Cancer Inst* 46(6):1335-1339, 1971.

Maternal and fetal tissues taken from 2 genotypes of strain HRS/J mice were cultured and tested for the presence of virus; the genotypes were the hairless type (*hr/hr*) and the haired type (+/+). Cultured fetal cells from individuals of the 2 genotypes grew as multiple layers of mixed epithelial and fibroblast-like cells. The *hr/hr* cells grew more slowly than the +/+ cells but both cell types exceeded the 50th passage generation. Ovary and placenta from maternal *hr/hr* female mice contained C-type budding virus particles but spleen did not; fetuses taken from *hr/hr* mothers were negative for C-type particles. Spleen, placenta and uterus from +/+ mothers were positive for C-type particles, as was 1 of 3 +/+ fetuses. Viruses released from cells of both types of mouse were typical murine C-type viruses. The RNA of viruses in *hr/hr* and +/+ cells was typical of murine leukemia virus RNA.

0118 INDUCTION OF LEUKEMIA IN WEANLING C3H/Bi MICE BY MEANS OF SKIN TRANSPLANTATION FROM PRELEUKEMIC DONORS. (E.) Mariani, T. (Pediatrics Dept., U. Minnesota, Minneapolis), Y. Maruyama and R. A. Good. *Proc Soc Exp Biol Med* 137(2):513-515, 1971.

Strain C3H/Bi mice, 2-5-days-old, were given intrathymic inoculations of 0.05 ml Gross passage A virus; when recipients had attained a pre-leukemic state skin grafts were prepared from them and implanted on C3H/Bi weanling mice. All of 49 weanling mice receiving grafts from preleukemic mice died of leukemia; the mean latency for leukemia onset was 174 days. Forty-one of the 49 mice receiving grafts showed thymic enlargement. Of 10 mice given grafts of skin from normal mice none died of leukemia and none showed thymic enlargement.

0119 COMPARATIVE STUDIES ON MONOLAYER AND SUSPENSION CELL CULTURES FROM A TRANSPLANTABLE RAT MAMMARY CARCINOMA CONTAINING C-TYPE VIRUS

PARTICLES. (E.) Guest, G. B. (Sch. Veterinary Med., U. Pennsylvania, Kennett Square), P-S. Lin, N. D. Stock, R. M. Dutcher and G. C. Engle. *Oncology* 25(2):104-118, 1971.

When cells from an X-irradiation-induced transplantable rat mammary carcinoma were used to establish monolayer cultures the cell density increased in the 4-5 days following culture initiation; confluent monolayers, however, could not be permanently established and after the 5th day cell density began to decrease. Cells cultured with horse serum agglutinated into clumps. Mammary tumor cells could be established in suspension cell cultures. Cells in suspension cultures clumped when treated with horse serum but did not clump when treated with fetal calf serum. Tumor cells constituting the short-term monolayer cultures were of 2 main types: a spindle shaped cell and an epithelial-like cell. Both cell types showed basophilic staining properties with a mildly granular cytoplasm; tumor cells stained more densely than normal rat embryo cells. Tumor cells showed a larger nucleus, and had relatively less cytoplasm than did cells in monolayer cultures. The modal chromosome number of tumor cells was 45; tumor cells showed 1 large submetacentric chromosome, 1 medium metacentric and 2 small acrocentric chromosomes. Tumor cells in short term monolayer cultures, and tumor cells which had been 151 days in suspension cultures, were found to contain C-type virus particles when examined under the electron microscope.

0120 APPEARANCE OF VIRUS PARTICLES IN BALB/c MAMMARY NODULE OUTGROWTH LINES TRANSPLANTED INTO BALB/cf. C3H AND (C3Hf x BALB/c)<sub>F1</sub> MICE. (E.) Medina, D. (Dept. Zool., U. California, Berkeley), K. B. DeOme, D. R. Pitelka and V. B. Colley. *J Nat Cancer Inst* 46(6):1153-1160, 1971.

Mammary nodule outgrowth cells from BALB/c mice were transplanted into a strain of mammary tumor virus (MTV)-harboring mice (BALB/cf C3H) and into a strain of nodule-inducing virus (NIV)-harboring mice (C3Hf x BALB/c)<sub>F1</sub>; in some cases recipient mice had undergone hormonal stimulation by means of pituitary isografts. The times at which MTV or NIV particles appeared in mice given implants of the mammary nodule outgrowth cell lines (designated D1 and D2) were noted. Virus particles were found from 8-11 wk after transplantation in outgrowths transplanted into BALB/cf C3H mice; in hormone-stimulated mice of this strain, virus particles appeared at about the same time. Virus particles were not found in the outgrowths in (C3Hf x BALB/c)<sub>F1</sub> mice until 44 wk after transplantation; when mice of this strain were stimulated by pituitary isografts prior to transplantation, virus particles appeared by 26 wk after transplantation. In a related experiment, D1 outgrowths were transplanted into 21-wk-old mice and virus particles appeared 23 wk after transplantation; in mice which had been hormonally stimulated for 18 wk before transplantation, virus particles appeared within 13 wk after transplantation.

0121 SPECIFICITY OF THE DNA PRODUCT OF THE C-TYPE VIRUS RNA-DEPENDENT DNA POLYMERASE. (E.) Hatanaka, M. (Flow Labs., Inc., Rockville, Md.), R. J. Huebner and R. V. Gilden. *Proc Nat Acad Sci USA* 68(1):10-12, 1971.

Hybridization experiments were performed using RNA of C-type virions, including AKR mouse virus, cat virus, viper virus and hamster virus; the specificity of the DNA product of the RNA-dependent DNA polymerase in the viruses was investigated. In all hybridization experiments performed under annealing conditions a portion of the homologous DNA showed a clear shift in density toward the region of viral RNA. When homologous DNAs were replaced with heterologous DNAs no evidence of specific annealing was seen. Tests revealed a clear species specificity for the DNA product, with no interspecies hybridization in evidence.

0122 CELLULAR INTERACTIONS *IN VITRO* WITH CELLS DERIVED FROM TUMORS INDUCED BY MURINE SARCOMA VIRUS (HARVEY). (E.) Simons, P. J. (Sch. Med., U. Western Australia, Perth, Western Australia), A. A. Tuffery, D. J. McCully and E. J. Aw. *J Nat Cancer Inst* 46(6):1229-1242, 1971.

Sarcomas were induced in Prince Henry mice by inoculation with Harvey murine sarcoma virus and cells from these sarcomas were established in culture; cells from some of the cultures were cloned on collagen-coated dishes. Cultured sarcoma cells were of 3 types: numerous macrophages with lightly staining cytoplasm and nuclei; small cells with hyperchromatic nuclei, and large well-spread fibroblastic cells. At the 9th passage of the sarcoma cells, macrophages had disappeared and large clusters of cells had formed with a connecting network of spindle cells. Large multinucleate cells with vacuolated cytoplasm were scattered throughout the cultures. By the 44th passage the cultures were largely stable; cells showed nuclear pleomorphism and prominent mitotic activity. In cells grown in collagen, well-separated fibroblastic cells and spindle cells were seen; with continued passage, spindle cells increased in number. Multinucleate cells were numerous. In individual colonies of cells grown on collagen, cultures consisted of spindle cells; multinucleate strap cells became increasingly prominent as cultures neared confluence. Myokinase and creatine phosphokinase were assayed in cloned cells growing on collagen; as numbers of cells increased and more extensive multinucleate cells were formed, the activities of the 2 enzymes increased. Cells of the parent culture released murine sarcoma virus at all passages; clones of cells growing on collagen also produced virus, but the titers of virus produced varied from clone to clone.

0123 MURINE SARCOMA AND LEUKEMIA VIRAL INFECTION OF MICE: EFFECT OF LONG-TERM TREATMENT WITH POLY I:POLY C. (E.) Sarma, P. S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.),



R. H. Neubauer and L. S. Rabstein. *Proc Soc Exp Biol Med* 137(2):469-472, 1971.

NIH Swiss strain mice were inoculated s.c. at birth with 100 µg of polyinosinic polycytidylic RNA (poly I.poly C) and, on the following day, were inoculated s.c. with Moloney murine sarcoma virus (M-MSV); treatment was continued on alternate days for 80 days. Virus-inoculated mice not given poly I.poly C developed sarcoma in 63% of cases and lymphoma in 11.5% of cases, while virus-inoculated mice treated with poly I.poly C developed sarcomas in less than 1% of cases and developed lymphoma in 12.3% of cases. Spleens of virus-inoculated mice treated with poly I.poly C showed viral CF antigens, as did spleens of untreated virus-inoculated mice. Infectious murine leukemia virus was found in spleens of mice given poly I.-poly C as well as in spleens of untreated mice. In a related experiment, newborn mice were given poly I.poly C treatments followed by injections of Rauscher and Friend leukemia viruses. Poly I.poly C treatment suppressed the development of CF viral antigen in spleens of mice inoculated with 25 mouse infectious U of virus or less.

0124 MORPHOLOGICAL TRANSFORMATION OF MOUSE AND RAT EMBRYO CELLS *IN VITRO* BY AN AGENT FROM S37 ASCITES TUMOUR. (E.) Rasheed, S. (Mount Vernon Hosp. and Radium Inst., Northwood, Middlesex, England). *Brit J Cancer* 25(1):142-148, 1971.

Embryo cell cultures of hamster, BALB/c mice, and rats were inoculated with 1-4 doses of cell-free extract from an S37 ascites tumor passaged in BALB/c mice; inoculation of hamster cell cultures produced only cytopathic effects while inoculation of mouse or rat embryo cells induced cell transformation after 3.5-4.5 wk postinoculation. Transformed cells proliferated in suspension cultures while untransformed cells were incapable of sustained multiplication in suspension cultures. Normal untransformed cells showed contact inhibition of multiplication while transformed cells did not show contact inhibition. When transformed mouse and rat embryo cells were inoculated into mice and rats, 88% of inoculated mice developed tumors; however, only 2 of 67 inoculated rats developed tumors. Splenomegaly developed in most inoculated mice but in none of the inoculated rats. Tumors which developed in mice and rats inoculated with transformed cells were lymphosarcomas. The oncogenic agent in the transformed embryo cells was thought to be similar to the mouse sarcoma virus isolated from animals with Moloney virus-induced leukemia.

0125 REPLICATION OF ROUS SARCOMA VIRUS AND THE BIOSYNTHESIS OF THE ONCOGENIC SUBVIRAL RIBONUCLEOPROTEIN PARTICLES ("VIROSOMES") IN THE MITOCHONDRIA ISOLATED FROM ROUS SARCOMA TISSUE. (E.) Kara, J. (Czechoslovak Acad. Sci., Prague), O. Mach and H. Cerna. *Biochem Biophys Res Commun* 44(1):162-170, 1971.

Tumors induced in chickens by Rous sarcoma virus (RSV) were excised and mitochondria were isolated and labeled with uridine-5-<sup>3</sup>H. The labeled Rous sarcoma mitochondria were disrupted and analyzed by zonal centrifugation in a sucrose density gradient. Incorporated radioactivity in tumor cells was found in the fraction containing the mitochondrial membranes at a density of 1.17. Radioactivity was also found in fractions of density 1.16, the density of RSV; low radioactivity was found in fractions of density 1.19. Viral infectivity was present mainly in fractions of density 1.16 and 1.17, a finding which indicated that free RSV and RSV bound to mitochondrial membranes were present. Chick embryo fibroblast transforming capacity was associated with the mitochondrial fraction with density 1.28; oncogenic viral ribonucleoprotein particles, synthesized in isolated mitochondria, were present in this fraction. When young chickens were injected with cells infected with this fraction, tumors developed in 75% of the birds within 6 weeks. Tumors were typical RSV-producing Rous sarcomas. It was concluded that RSV is present and replicated with mitochondria isolated from Rous sarcoma cells.

0126 INDUCTION OF RHABDOMYOSARCOMAS IN MAMMALS WITH A HIGHLY ONCOGENIC VARIANT OF ROUS SARCOMA VIRUS. (E.) Obukh, I. B. (Acad. Med. Sci. U.S.S.R., Moscow), I. S. Levenbook, I. N. Kryukova and T. I. Biryulina. *Folia Biol (Praha)* 17(3):175-181, 1971.

A variant of Rous sarcoma virus designated Carr-Zilber virus number 1 was isolated from mouse embryo tissue cells, passaged in chickens, and inoculated into rats, Af strain mice, rhesus monkeys and green monkeys. Other animals were inoculated with the conventional Carr-Zilber Rous virus; Carr-Zilber virus number 1 was found to be more oncogenic for adult rats and monkeys than the conventional virus. None of the 5 rats which were given conventional virus developed tumors while all 20 rats given Carr-Zilber virus number 1 developed tumors. Tumors were s.c. nodules which had the histological properties of poorly differentiated rhabdomyosarcomas. Tumors developing in mice given Carr-Zilber virus number 1 were classified as rhabdomyoblastomas of the epithelioid cell type. Lung metastases were seen in some of these mice. All monkeys given Carr-Zilber virus number 1 developed tumor nodules at the site of injection within 12-18 days after virus inoculation; no metastases were seen however. Tumors in rhesus monkeys contained group-specific antigens of the avian sarcoma leukosis complex.

0127 PRESENCE OF ROUS SARCOMA VIRUS INSIDE THE MITOCHONDRIA ISOLATED BY ZONAL AND DIFFERENTIAL CENTRIFUGATION FROM ROUS SARCOMA CELLS. (E.) Mach, O. (Czechoslovak Acad. Sci., Prague) and J. Kara. *Folia Biol (Praha)* 17(2):65-72, 1971.

Sarcomas were induced in chickens by inoculating them with Schmidt-Ruppin strain Rous sarcoma virus;



tumor tissue was then subjected to zonal centrifugation. Virus activity was detected in 2 bands having densities of 1.16 g/cm<sup>3</sup> and 1.192 g/cm<sup>3</sup>; the latter band represented the mitochondrial fraction which contained Rous sarcoma virus. Virus from this fraction was used to infect chick embryo fibroblast cultures; 50% of infected cells were transformed by 5 days postinfection. When infected chick embryo fibroblasts were centrifuged, virus activity was again found in fractions having densities of 1.16 and 1.192 g/cm<sup>3</sup>. The results were thought to suggest that mitochondria participate in the development of infectious Rous sarcoma virus.

- 0128 TUMOUR INDUCTION BY SIMIAN ADENOVIRUS SA7 DNA FRAGMENTS. (E.) Mayne, N. (Lilly Res. Lab., Indianapolis, Ind.), J. P. Burnett and L. K. Butler. *Nature* 232(32):182-183, 1971.

Light and heavy fragments of DNA from Simian adenovirus 7 were produced by sonication and centrifugation and subjected to ultracentrifuge analysis. The buoyant densities of the separated light and heavy fragments corresponded to 54.6 and 61.6% guanine + cytosine, resp. Newborn hamsters were inoculated with 5 µg intact DNA, 3 µg of intact denatured DNA, or 5 µg of sheared DNA, sheared DNA heavy fragments, or sheared DNA light fragments. Intact simian adenovirus 7 DNA produced tumors in 3 of 22 hamsters after 107 or 115 days; intact denatured DNA produced no tumors in 22 hamsters. Heavy DNA fragments produced 5 tumors in 25 hamsters after 51-136 days and light DNA fragments produced 4 tumors in 19 hamsters after 51 or 129 days. The results may suggest that the entire viral genome is not required for oncogenesis, 1 of several regions of the genome sufficing to produce tumors.

- 0129 INFLUENCES OF CELL CYCLE ON UPTAKE OF SV40-DNA BY DIPLOID HUMAN CELLS. (E.) Mukerjee, D. (U. Texas Med. Brnch., Galveston) and J. M. Bowen. *Experientia* 27(5):560-562, 1971.

Cultures of human diploid cells taken from skeletal muscle tissue were synchronized by arresting cell development at the S, M and G<sub>1</sub> phases; synchronized cultures were infected with tritium-labeled SV40; virus retention was determined when the infected cells were about to enter other phases of the cell cycle. Cells infected with labeled virus at M and G<sub>1</sub> did not retain significant amounts of the virus label. Cells infected at S but harvested after 4 and 6 hr from the onset of the infection period retained labeled virus primarily in cytoplasm, whereas cells infected with labeled virus in the S phase and harvested 8 hr after infection showed accumulations of labeled virus within the nucleus. Cells infected in the S phase and arrested at metaphase retained the labeled virus primarily on the chromosomes.

- 0130 INTERFERON AND TRANSCRIPTION OF EARLY VIRUS-SPECIFIC RNA IN CELLS INFECTED WITH SIMIAN VIRUS 40. (E.) Ozman, M. N. (Harvard Med. Sch., Boston, Mass.) and M. J. Levin. *Proc Nat Acad Sci USA* 68(2):299-302, 1971.

African green monkey kidney cells (AGMK) and Vero monkey cells were infected with SV40 and treated with interferon prepared from human leukocytes and/or from AGMK cells. Human interferon reduced SV40 T antigen formation by 66% in AGMK cells and by 96% in Vero cells. Monkey interferon reduced SV40 T antigen formation by 96% in Vero cells when added to cultures in amounts of 20 U/ml and by 99% when added in amounts of 50 U/ml. In addition, virus-specific RNA (cRNA), as measured by either the proportion of input RNA hybridizing with SV40 DNA or by the total SV40 content of RNA hybridizing to a complementary DNA, appeared markedly reduced in cultures treated with interferon. SV40 cRNA was reduced 54% in AGMK cells treated with human interferon and 82% in Vero cells treated with human interferon. AGMK interferon reduced SV40 cRNA in Vero cells by 92%.

- 0131 COMPARATIVE STUDIES OF SV40 AND ADENOVIRUS ONCOGENESIS IN RANDOM BRED AND INBRED HAMSTERS. (E.) Larson, V. M. (Merck Inst. Therapeutic Res., West Point, Pa.), W. R. Clark and M. R. Hilleman. *Proc Soc Exp Biol Med* 137(2):607-613, 1971.

Newborn random bred (strain LVG/LAK) and inbred (strains MHA/SsLaK and LSH/SsLaK) hamsters were inoculated s.c. in the scapular region with undiluted SV40 or adenovirus; some animals were given 1:2 dilutions of virus. Tumors developing on inoculated hamsters were transplanted to hamsters of the same strain. Thirty-four percent of inbred MHA hamsters given SV40 developed tumors while 95% of the inbred LSH hamsters, and 84% of the random bred LVG hamsters, developed tumors following SV40 inoculation. Adenovirus type 7 failed to produce tumors in MHA hamsters, but did produce tumors in 7% of LSH and in 11% of LVG hamsters. Adenovirus type 12, tested only in LSH and LVG hamsters, induced tumors in 87% of the former strain and in 90% of the latter. Readily transplantable tumor lines were established from all the virus-induced tumors; transplants from tumors arising on MHA hamsters given SV40 showed longer latent periods for transplant take than did transplants taken from other lines. All the primary SV40-induced tumors were fibrosarcomas; hamsters given adenovirus types 7 or 12 developed undifferentiated sarcomas which in some cases resembled malignant lymphomas.

- 0132 TEMPERATURE-DEPENDENT SURFACE CHANGES IN CELLS INFECTED OR TRANSFORMED BY A THERMOSENSITIVE MUTANT OF POLYOMA VIRUS. (E.) Eckhart, W. (Salk Inst. Biol. Studies, San Diego, Calif.), R. Dulbecco and M. M. Burger. *Proc Nat Acad Sci USA* 68(2):283-286, 1971.

BALB/3T3 mouse cells were infected with wild type polyoma virus or with a temperature-sensitive mutant of polyoma virus (ts-3); infected cells were treated with wheat germ agglutinin in amounts of 36-180 µg/ml, and the agglutination of virus-infected cells was observed in cultures grown at 39 and 32°C. Enhanced agglutination was seen in cells infected with ts-3 and grown at 32°C but not in cells infected with ts-3 and grown at 39°C. Enhanced agglutination was seen in cells infected with wild-type polyoma virus and grown at either temperature. It was found that agglutination enhancement required cellular DNA synthesis but did not require viral DNA synthesis. In a related experiment, baby hamster kidney cells transformed by ts-3 were tested for agglutination by agglutinin and concanavalin A (Con A) after being grown at 39 and 32°C. Ts-3-transformed cells showed increased agglutinability when grown at 32°C, but not when grown at 39°C. The viral gene apparently controls the surface alteration responsible for changing agglutinability in virus-transformed cells.

0133 BIOCHEMICAL GENETICS OF HUMAN BLOOD-GROUP MN SPECIFICITIES AND THEIR RELATION TO INFECTIOUS MONONUCLEOSIS- AND ONCOGENIC VIRUS-RECEPTORS. (E.) Springer, G. F. (Evanston Hosp., Evanston, Ill.), S. V. Huprikar and H. Tegtmeyer. *Z Immunitätsforsch* 142(1):99-102, 1971.

0134 HAEMAGGLUTINATION REACTION WITH AVIAN MYELOBLASTOSIS-VIRUS. (E.) Szanto, J. (Slovak Acad. Sci., Bratislava, Czechoslovakia). *Acta Virol* 15(3):245-248, 1971.

0135 CELLULAR IMMUNITY INDUCED BY ROUS SARCOMA VIRUS IN JAPANESE QUAIL: II. EFFECT OF THYMECTOMY AND BURSECTOMY ON ONCOGENESIS OF ROUS SARCOMA VIRUS. (E.) Yamanouchi, K. (Nat'l. Inst. Hlth., Tokyo, Japan), M. Hayami, S. Miyakura, A. Fukuda and F. Kobune. *Jap J Med Sci Biol* 24:1-8, 1971.

0136 MULTIPLICATION OF THE HERPES SIMPLEX VIRUS IN γ-IRRADIATED HUMAN CELL CULTURES. (Rus.) Andonov, P. (Inst. Radiol. Radiat. Hygiene, Sofia, Bulgaria), S. Todorov, S. Dundarov, B. Ivanov and Ye. Mineva. *Radiobiologiya* 11(2):224-229, 1971.

0137 PERIPHERAL BLOOD ALTERATIONS IN MICE IN-OCULATED WITH CELL-FREE FILTRATES FROM GRAFFI VIRUS-INDUCED LEUKEMIA. (Pol.) Niezabitowski, A. (Acad. Med., Cracow, Poland). *Pat Pol* 22(2):239-249, 1971.

0138 MASON-PFIZER MONKEY VIRUS ISOLATED FROM SPONTANEOUS MAMMARY CARCINOMA OF A FEMALE MONKEY: I. DETECTION OF VIRUS ANTIGENS BY IMMUNODIFFUSION, IMMUNOFLUORESCENT, AND VIRUS AGGLUTINATION TECHNIQUES. (E.) Ahmed, M. (Pfizer, Inc., Maywood, N. J.), S. A. Mayyasi, H. C. Chopra, I. Zelljadt and E. M. Jensen. *J Nat Cancer Inst* 46(6):1325-1330, 1971.

0139 SELECTIVE LYSIS OF CELLS TRANSFORMED BY ROUS SARCOMA VIRUS. (E.) Rifkin, D. B. (Rockefeller U., New York, N. Y.) and E. Reich. *Virology* 45(1):172-181, 1971.

0140 VIRAL AND CHEMICAL LEUKEMIA IN THE RAT: COMPARATIVE STUDY. (E.) Ioachim, H. L., (Lenox Hill Hosp., New York, N. Y.), M. Sabbath, B. Andersson and S. Keller. *J Nat Cancer Inst* 47(1):161-168, 1971.

0141 THE ROLE OF EPSTEIN-BARR VIRUS IN INFECTIOUS MONONUCLEOSIS AND IN MALIGNANT TUMORS. (Ger.) Goetz, O. (Ped. Clin. U. München, Germany) and P. Peller. *Mtschr Kinderheilk* 119(7):324-327, 1971.

0142 DIFFERENTIAL SUSCEPTIBILITY OF TWO CELL TYPES TO THE CHROMOSOME-BREAKING EFFECTS OF ADENOVIRUS TYPE 5. (E.) Nichols, W. W. (Inst. Med. Res., Camden, N. J.), A. Levan, L. Kjellen and S. Sheldon. *Mutat Res* 12(2):191-196, 1971.

0143 SPONTANEOUS AND ADENOVIRUS TYPE 12-INDUCED CHROMOSOME ABERRATIONS IN FANCONI'S ANAEMIA FIBROBLASTS. (E.) McDougall, J. K. (Dept. Cancer Studies, U. Birmingham, Birmingham, England). *Int J Cancer* 7(3):526-534, 1971.

0144 PATHOLOGICAL ANATOMY AND ULTRASTRUCTURE OF ORGAN TISSUES IN MAREK'S DISEASE. (SP.) Garcia Partida, P. (No affiliation), S. Gonzalez and Gonzales, J. Sanz Esponera. *Rev Esp Oncol* 16(2):159-174, 1969.

0145 PLAQUE FORMATION BY YABA VIRUS IN CYNOMOLGUS MONKEY KIDNEY CELLS. (E.) Tsuchiya, Y. (Dept. Microbiol., S. Illinois U., Carbondale) and H. Rouhandeh. *J Nat Cancer Inst* 47(1):219-221, 1971.



# VIRAL CARCINOGENESIS

0146 FURTHER STUDIES ON THE REPLICATION OF  
MAREK'S DISEASE VIRUS IN THE CHICKEN AND  
IN CELL CULTURE. (E.) Nazerian, K. (U.S. Dept.  
Agric., Lansing Mich.). *J Nat Cancer Inst* 47(1):  
207-212, 1971.

0147 POLYPEPTIDES OF AVIAN RNA TUMOR VIRUSES:  
III. PURIFICATION AND IDENTIFICATION OF A  
DNA SYNTHESIZING ENZYME. (E.) Moelling, K. (Max-  
Planck Inst. Virus Res., Tübingen, Germany), D. P.  
Bolognesi and H. Bauer. *Virology* 45(1):298-302,  
1971.

0148 REGULATION OF DNA SYNTHESIS IN MACROPHA-  
GES INFECTED WITH SIMIAN VIRUS 40. (E).  
Lehman, J. M. (Wistar Inst., Philadelphia, Pa.),  
J. MaueI and V. Defendi. *Exp Cell Res* 67(1):230-  
233, 1971.

0149 DEOXYRIBONUCLEIC ACID POLYMERASE ASSOCIAT-  
ED WITH FELINE LEUKEMIA AND SARCOMA VIRUS-  
ES: PROPERTIES OF THE ENZYME AND ITS PRODUCT. (E).  
Roy-Burman, P. (U. Southern California Sch. Med.,  
Los Angeles). *Int J Cancer* 7(3):409-415, 1971.

See also:

- \* (Rev): 0002, 0003, 0017, 0022, 0028
- \* (Chem): 0059
- \* (Immun): 0153, 0165, 0175



(0146-0149)

- 0150 INDUCTION OF TUMOR IMMUNITY IN MICE WITH ANTIGENS PREPARED FROM INFLUENZA AND VESICULAR STOMATITIS VIRUS GROWN IN SUSPENSION CULTURE OF EHRLICH ASCITES CELLS. (E.) Häkkinen, I. (Dept. Virol., U. Turku, Finland) and P. Halonen. *J Nat Cancer Inst* 46(6):1161-1167, 1971.

BALB/c strain mice were immunized with either concentrated or unconcentrated influenza virus grown in Ehrlich ascites tumor cell cultures; 11 days later, mice were challenged with 1000 Ehrlich ascites cells; after 5 days a second challenge dose of 100,000 Ehrlich cells was administered to the immunized mice. All mice immunized with concentrated influenza virus were immune to the challenge and 1 of 6 mice immunized with unconcentrated virus developed s.c. tumors. Unimmunized mice challenged with 100,000 Ehrlich cells developed tumors in all cases. In a related experiment, mice were immunized with live influenza virus or with virus inactivated by UV or formaldehyde. No tumor growth following challenge with Ehrlich cells was seen in mice immunized with formaldehyde-inactivated virus. UV-inactivated influenza virus did not confer immunity as effectively as did formaldehyde-inactivated virus. In these experiments, concentrated influenza virus was not as immunogenic as unconcentrated virus. In identical experiments using vesicular stomatitis virus (VSV) grown in Ehrlich cell cultures as antigen, unconcentrated UV-inactivated VSV proved to be more effective in conferring immunity to Ehrlich cell challenge than formaldehyde-inactivated unconcentrated virus, concentrated live VSV, or unconcentrated live VSV. VSV grown in baby hamster kidney cell cultures did not confer immunity to Ehrlich cell challenge. Sonically disrupted Ehrlich cells used to immunize mice against a subsequent challenge with Ehrlich cells produced immunity to challenge in 1 of 6 mice only.

- 0151 TUMOUR IMMUNITY INDUCED IN MICE WITH CELL-FREE HOMOGENATES OF INFLUENZA VIRUS-INFECTED TUMOUR CELLS. (E.) Boone, C. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.), K. Blackman and P. Brandschaft. *Nature* 231(5300):265-266, 1971.

Mice of the BALB/c strain were immunized with influenza virus-infected cells from a murine SV40-induced tumor 14 days prior to challenge with  $10^6$  syngeneic tumor cells not infected with influenza virus. Almost complete protection against tumor challenge was induced by immunization with  $10^{-1}$  and  $10^{-2}$  dilutions of influenza virus-infected tumor cell homogenates and partial protection was induced by immunization with a  $10^{-3}$  dilution (2 of 35 mice given the  $10^{-1}$  dilution developed tumors). In contrast, mice vaccinated with tumor cells which had not been infected with influenza virus were not protected against challenge (20 of 26 mice in this group developed tumors upon challenge). In addition, mice vaccinated with normal mouse cells infected with influenza virus were not rendered immune (15 of 17 mice in this group developed tumors).

- 0152 TOLERANCE INDUCTION IN ADULT MICE WITH TUMOR HOMOGRAFTS. (E.) Wachtel, S. S. (Sch. Med., U. Pennsylvania, Philadelphia) and W. K. Silvers. *Transplantation* 12(1):61-64, 1971.

Five CBA strain mice were inoculated either with cells from a spontaneous mammary adenocarcinoma from a C3H strain mouse or with C3H spleen cells; tumors regressed by 2 wk postinoculation in the former group. Fifty days after the injection, the mice were challenged with a skin graft from a male C3H mouse; all the mice given spleen cells and 4 of the 5 mice given tumor cells rejected the graft within 10 days. The fifth graft recipient developed a tumor which was successfully passaged to CBA mice. In a related experiment, 6 CBA mice were inoculated s.c. with cells from a (CBA x C3H) $F_1$  mammary tumor and thereafter challenged with C3H mouse skin grafts. The graft survived for a prolonged period in 1 recipient. The unresponsiveness induced by the tumors to subsequent skin grafts was apparently specific for C3H mouse tissues, and was not related to a general physical debility of the graft recipients.

- 0153 A GROUP SPECIFIC ANTIGEN OF MOUSE LEUKEMIA VIRUSES: IMMUNOLOGICAL AND HISTOCHEMICAL STUDIES. (Rus.) Lezhneva, O. M. (N. F. Gamaleya Inst. Epidemiol. and Microbiol., Moscow, U.S.S.R.) G. I. Abelev. *Vop Virus* 16(3):348-352, 1971.

A method for preparing monospecific antibodies against the group-specific antigen (GSA) of murine leukemia viruses is presented. The antibodies thus obtained allow detection of a group-specific antigen in normal and tumor cells of different mouse lines using an indirect immunofluorescence method. Adult mice of the AKR, BALB/c, B10D2, CC57BR, CC57W, Af and C57BL10/572 lines were used. Rauscher leukemia was first induced with a Rauscher virus in BALB/c mice and then passaged on the same mice. Transplantable sarcomas were induced with methylcholanthrene and a second sarcoma was induced with a Rauscher virus. GSA was contained in the  $\gamma$ -globulin fraction obtained by electrophoresis from Rauscher leukemic sera. Rabbit antiserum for Rauscher virus, depleted with plasma from healthy mice, was used for the preparation of antibodies against the GSA. Indirect fluorescence was applied to slice preparations from leukemic BALB/c mouse spleens and from normal spleens of mice from the other 6 lines to preparations from 10 solid tumors from 5 mouse lines, to kidney preparations from AKR and BALB/c mice and to a spleen preparation from a Wistar rat. Treatment with GSA antibody extracts produced pronounced fluorescence in leukemic mouse spleen and in normal AKR mouse spleen cells; less intense positive reactions were given by preparations from normal spleens of Af, CC57BR and C57BL10/572 mice. Normal spleen preparations from BALB/c mice gave a negative and then a weak positive reaction. The spleen preparations from B10D2 mice and from the Wistar rat gave negative reactions. The specificity of the reaction was verified by treatment of the preparations with an anti-GSA extract, previously neutralized with pure GSA; by treatment with normal

rabbit  $\gamma$ -globulin or with labeled extract of donkey antibodies. The precipitin and immunofluorescence reactions appeared to be consistent. Discrepancy between the 2 reactions was noticed in 1 of 10 tested solid tumors and in 1 normal BALB/c spleen preparation and was attributed to the different sensitivities of the 2 methods.

- 0154      ENHANCEMENT BY PITUITARY ISOGRAFTS OF MAMMARY HYPERPLASTIC NODULES IN ADRENO-OVARECTOMIZED MICE. (E). Yanai, R. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan) and H. Nagasawa. *J Nat Cancer Inst.* 46(6):1251-1255, 1971.

Multiparous female mice of the C3H/He strain were bilaterally adreno-ovariectomized; some mice were given no further treatment and some were given grafts of 1.5 or 3 pituitary glands under the right kidney capsule. A fourth group of mice was given no treatment of any kind (intact controls). Twenty-five mammary hyperplastic nodules (HN) developed/mouse in 27 intact controls and 7 HN developed/mouse in 8 adreno-ovariectomized mice not given pituitary isografts. Nineteen HN developed/mouse in 10 mice given adreno-ovariectomy and 1.5 pituitary isografts, and 32 HN developed/mouse in 15 mice given adreno-ovariectomy and 3 pituitary isografts. The average size of HN was larger in mice with 3 pituitary grafts than in intact controls.

- 0155      CELLULAR IMMUNITY, ITS SERUM MEDIATED INHIBITION AND TUMOR-DISTINCTIVE ANERGY TO TUMORS IN MAN. (E.) Stjernsward, J. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden) and F. Vanky. *Advances Exp Med Biol* 12:545-553, 1971.

An investigation was carried out to determine the extent to which cellular immunity against autochthonous cancer exists in the cancer patient with active disease. Results obtained by a "mixed-lymphocyte-target-interaction-test" (MLTI-test) indicated that the peripheral lymphocytes of the cancer patient mixed *in vitro* with autochthonous malignant or non-malignant cells in which DNA synthesis had been blocked were stimulated to increased DNA synthesis more often and to a greater extent by neoplastic than by non-neoplastic autochthonous cells. Lymphocytes from 40 of 105 patients showed stimulation of DNA synthesis (Burkitt lymphoma 5/8, renal carcinoma 10/16, nasopharyngeal carcinoma 3/4, thyroid carcinoma 2/2, breast carcinoma 1/5, testis carcinoma 2/3, reticulum cell sarcoma 1/1, osteogenic sarcoma 2/4, soft tissue sarcoma 11/36, malignant melanoma 1/1, primary brain tumor 2/15). The reactivity of peripheral lymphocytes against autochthonous tumor cells was reduced by prior incubation in 5 of 9 patients tested; this result was thought to indicate that serum-bound factors may block the cellular immunity of certain patients. Stimulation of DNA synthesis by autochthonous tumor cells occurred in lymphoid cells from nodes draining a large tumor (0/5), in lymphoid cells from

nodes exposed to small doses of irradiated tumor cells (5/16), and in lymphoid cells from nodes remote from a tumor (1/14). The behavior in these tests of lymphoid cells from nodes draining large tumors was thought to evidence tumor distinctive immunological energy.

- 0156      CELLULAR IMMUNITY TO HUMAN SARCOMA. (E). Vanky, F. (Karolinska Inst., Stockholm, Sweden), J. Stjernsward and U. Nilsson. *J Nat Cancer Inst* 46(6):1145-1151, 1971.

Peripheral lymphocytes from the blood of patients with benign and malignant tumors were mixed with  $1 \times 10^6$  mitomycin-C-treated autochthonous tumor cells in order to determine whether the lymphocytes would be stimulated to enhanced DNA synthesis. Autochthonous tumor cells from patients with benign tumors did not stimulate DNA synthesis in peripheral lymphocytes; the reactivity index of lymphocytes mixed with autochthonous benign cells did not exceed 1.3. In 13 of 26 patients with malignant tumors (sarcomas), peripheral lymphocytes showed increased DNA synthesis exceeding a reactivity index of 1.5 after treatment with autochthonous tumor cells. In 4 of these patients, the reactivity index was between 1.5-2.0 and in 6 it was between 2.0 and 5.0. Three patients, 2 with fibrosarcoma and 1 with rhabdomyosarcoma, had reactivity indices exceeding 5.0 for peripheral lymphocytes treated with autochthonous tumor cells. Frozen tumor cells stimulated lymphocyte DNA synthesis, as did fresh tumor cells.

- 0157      ATTEMPT AT EVALUATION OF DEFENSIVE ACTIVITY OF LYMPH NODES ON THE BASIS OF MICROSCOPIC AND CLINICAL STUDIES IN CASES OF LARYNGEAL CANCER. (E.) Malicka, K. (Postgrad. Med. Educ. Ctr., Bydgoszcz, Poland). *Pol Med J* 10(1): 154-164, 1971.

Regional lymph nodes from 81 patients with laryngeal cancer were investigated microscopically; in 62 cases metastases were absent. In 19 cases, lymphonodular sinus histiocytosis was seen; the medullary sinuses were dilated and filled with reticular cells. In 36 cases, hyperplasia was evident and in 8 cases of mixed morphology a preponderance and proliferation of lymph nodes or a dilated system of sinuses and hyperplasia of the reticulo-endothelial system was prevalent. It was noted that lymph nodes without metastases and with sinus histiocytosis were often associated with a favorable clinical course, while lymph nodes showing hyperplasia were generally associated with a poor prognosis. In lymph nodes showing metastases, metastatic foci were found to be separated from the lymphonodular tissue by a deposit of acid mucopolysaccharides which was absent in regions in which lymph nodes were not infiltrated by neoplastic tissue.

- 0158      IMMUNOFLUORESCENCE TESTS ON SERA OF PATIENTS WITH OSTEOGENIC SARCOMA. (E). Priori, E. S. (U. Texas M. D. Anderson Hosp.,



Houston), J. R. Wilbur and L. Dmochowski. *J Nat Cancer Inst* 46(6):1299-1306, 1971.

Imprints of 8 osteosarcomas and tissue culture cells derived from 11 other bone tumors were subjected to indirect immunofluorescence tests using sera from patients with osteosarcoma, from relatives of patients with osteosarcoma and from normal donors. Of the 8 imprints, 4 showed a positive reaction when tested with autologous serum; this indicated that these cells contained antibodies to osteosarcoma cells. In addition, 18 of 38 tests carried out on the 8 tumor imprints using sera from 6 patients with the same disease were positive. In 34 tests with sera from 8 relatives of the 5 original tumor imprint donors, 2 sera from maternal relatives were positive. None of the sera taken from 5 normal donors reacted with cells from the osteosarcoma imprints. Tissue culture cells used in immunofluorescence tests included 5 osteogenic sarcomas, 1 rhabdomyosarcoma, 1 Ewing's tumor, 1 chondrosarcoma and 2 giant cell tumors. Sera from 9 of the 18 patients with osteogenic sarcoma reacted with 1 or 2 of the osteogenic sarcoma cell cultures; sera from 10 of the 18 patients reacted with 1 or both of the giant cell tumor cell cultures. Ewing's tumor cells in culture failed to react with sera from any of the sources tested.

0159 COMPARISON OF THE CARBOHYDRATE PORTION OF MEMBRANE H-2 ALLOANTIGENS ISOLATED FROM SPLEEN CELLS AND TUMOR CELLS. (E.) Muramatsu, T. (Albert Einstein Coll. Med., Bronx, N.Y.) and S. C. Nathenson. *Biochim Biophys Acta* 241(1):195-199, 1971.

H-2 transplantation alloantigens from tumor and normal cells were found to be alike in terms of molecular size. [<sup>3</sup>H] Fucose and [<sup>3</sup>H] glucosamine-labeled glycopeptides obtained from 4-2 alloantigen glycoproteins from spleen cells of C57BL/6 and BALB/c strains of mice were found to have a molecular weight of approximately 3300 upon Sephadex column chromatography. This value appeared to be identical to the molecular size of glycopeptides from H-2 alloantigens isolated from a lymphoma cell line derived from the C57BL/6 mouse and a fibrosarcoma cell line derived from the BALB/c mouse. Elution profiles upon DEAE-Sephadex column chromatography appeared to be essentially identical for both H-2 alloantigen glycopeptides from spleen cells and those isolated from tumor cells. Apparently the disorder in malignant cells accounting for alterations in the overall glycoprotein pattern of Sephadex chromatography is not a general change occurring in all glycoproteins.

0160 ENHANCED TRANSFORMATION OF HUMAN IMMUNOCOMPETENT CELLS BY DIBUTYRL ADENOSINE CYCLIC 3',5'-MONOPHOSPHATE. (E.) Gallo, R. C. (Human Tumor Cell Biol. Brnch., Natl. Cancer Inst., Bethesda, Md.) and J. Whang-Peng. *J Natl Cancer Inst* 47(1):91-94, 1971.

Normal human lymphocytes and lymphocytes from patients with chronic lymphocytic leukemia were incubated with PHA and/or streptolysin I and incubation mixtures were treated with various amounts of dibutyryl cyclic 3',5'-monophosphate (AMP); DNA synthesis and percentage of lymphocytes transformed to "blast-like" cells were observed in the dibutyryl cyclic 3',5' AMP-treated cells. Concentrations of dibutyryl cyclic 3',5' AMP of 10<sup>-7</sup> and 10<sup>-6</sup> M enhanced transformation and DNA synthesis; in normal lymphocytes concentrations above 10<sup>-6</sup> inhibited transformation. In contrast, dibutyryl cyclic 3',5' AMP had no enhancing effects on lymphocytes from leukemia patients. Antigenic stimulation with streptolysin O produced an enhanced response in lymphocytes treated with dibutyryl cyclic 3',5' AMP; higher concentrations of dibutyryl cyclic 3',5' AMP did not have a marked inhibitory effect on transformation and had no inhibitory effect on DNA synthesis.

0161 ETIOLOGIC STUDY OF NASOPHARYNGEAL CANCER. (E.) Miller, D. (Harvard Med. Sch., Boston, Mass.), J. M. Goldman and M. L. Goodman. *Arch Otolaryng* 94(2):104-108, 1971.

Blood, drawn from 19 United States residents with nasopharyngeal carcinoma, was examined to determine the titers of anti-Epstein-Barr virus (E-B virus) antibody. Significantly positive antibody titers were found in 14 patients and ranged from 1:160-1:640 (the mean titer for all the 19 patients was 1:241). Ten patients with nonmalignant lesions of the nasopharynx showed a mean anti-E-B virus antibody titer of 1:37. The highest mean anti-E-B virus antibody titers were recorded in patients with lymphoepithelioma (1:363) of the nasopharynx; patients with squamous cell carcinoma of the nasopharynx had mean titers of 1:237. The findings were thought to suggest a causal connection between E-B virus and nasopharyngeal cancer.

0162 ENHANCED IMMUNOGENICITY OF CHEMICALLY-COATED SYNGENEIC TUMOR CELLS. (E.) Martin, W. J. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), J. R. Wunderlich, F. Fletcher and J. K. Inman. *Proc Nat Acad Sci USA* 68(2):469-472, 1971.

Mice of the C57BL/6 strain were given 2 i.p. injections of irradiated mouse lymphoid leukemia cells which had been coated with concanavalin A (Con A); 10 days after the second injection, mice were killed, their spleens were removed, and spleen cells were assayed for their ability to induce specific immune lysis of <sup>51</sup>Cr-labeled lymphoid leukemia or normal lymph node cells. Spleen cells from 1 of 8 mice injected with irradiated leukemic cells not coated with Con A induced lysis; by contrast, spleen cells from 7 of 8 mice immunized with Con A-coated leukemic cells induced lysis. In a related experiment, mice were given 2 injections of leukemic cells which had been coated with 6-(2,4-dinitrophenyl)aminocaproate (DnpC); spleens



were removed after 10 days and the immunogenicity of the coated leukemic cells was tested as in the first experiment. Antitumor activity was noted in spleen cells of mice given DnpC-coated leukemic cells. It was concluded that the immunogenicity of the strain of mouse lymphoid leukemia cells was enhanced by coating the cells with Con A or DnpC.

0163 HUMORAL ANTIBODIES OF RATS TREATED WITH A NONCARCINOGENIC ANALOGUE OF HEPATOTROPIC CARCINOGENIC AMINOAZO COMPOUNDS. (Rus.) Khundanova L. L. (N.N. Petrov Res. Inst. Oncol., Leningrad, U.S.S.R.). *Vop Onkol* 17(4):50-55, 1971.

The possible development of humoral antibodies in rats treated with diethylaminoazobenzene (DEAB), a noncarcinogenic structural analogue of the hepatotropic dimethylaminoazobenzene (DAAB) was investigated. DEAB was given in the diet (10 mg/day/rat) for 100 days and the sera were tested for antibodies after 4, 15, 30, 60 and 100 days of treatment; the data were compared to those obtained with sera from control (non-treated) and from carcinogen (DAAB)-treated rats. An increase in serum antibodies against normal liver antigens was observed after 4 days of DEAB treatment; this titer decreased during the following 15-100 days of treatment. Immuno-electrophoresis revealed 2 precipitin bands with normal liver antigen in the albumin and  $\alpha$ -globulin regions in sera of DEAB-treated rats and 1 band in the sera of control rats 4 days after the beginning of the experiment. The complement fixation reaction with normal liver antigens appeared to be positive (at each stage) in the sera of treated rats and negative in the sera of control rats. Four types of serum antibodies were observed during DAAB carcinogenesis: 1) against normal liver antigens, 2) against the complex carcinogen-protein antigens (occurring on the 4th day of carcinogen administration), 3) against anomalous antigens (occurring after 60-100 days of carcinogen treatment), and 4) against the hepatoma antigens. The 2 types of antibodies formed upon DEAB treatment were found to be directed against anomalous and normal liver antigens. Apparently, formation of humoral antibodies occurs upon the administration of noncarcinogenic compounds. Only certain specific antibodies occurring upon carcinogen administration seem to play a certain role in carcinogenesis.

0164 ANTIGENIC SPECIFICITIES ON MURINE SARCOMA CELLS: RECIPROCAL RELATIONSHIP BETWEEN NORMAL TRANSPLANTATION ANTIGENS (H-2) AND TUMOR-SPECIFIC IMMUNOGENICITY. (E.) Haywood, G. R. (U. Minnesota Med. Sch., Minneapolis) and C. F. McKhann. *J Exp Med* 133(6):1171-1187, 1971.

Monospecific H-2 antisera with 1 of 7 alloantigenic specificities were tested in quantitative absorption studies with cells from each of 5 methylcholanthrene-induced sarcomas of strain C3H mice. Each of the tumors showed either a high, medium or low surface representation of all of the 7 alloantigenic specificities tested; the number of tumor cells needed to absorb 50% of the antibody were determined. It

was seen that the tumor having minimal H-2 antigenicity required about 8 times more cells to absorb the same amount of antibody as was absorbed by the tumor having maximal H-2 antigenicity. No alloantigenic specificity was entirely lacking in any tumor, but no tumor showed an unusually large or small amount of any specificity. When the 5 tumors were tested for their capacity to induce a tumor-specific immune response in syngeneic mice, it was found that highly immunogenic tumors were tumors having relatively little H-2 surface antigen and that tumors of lesser immunogenicity were those having relatively large amounts of H-2 surface antigen. Tumors having low levels of tumor-specific immunity and correspondingly high levels of H-2 antigenicity produced early lung metastases when injected into syngeneic mice.

0165 IMMUNOLOGIC CROSS-REACTIVITY BETWEEN ANTIGEN OF UNFERTILIZED MOUSE EGGS AND MOUSE CELLS TRANSFORMED BY SIMIAN VIRUS 40. (E.) Koprowski, H. (Wistar Inst., Philadelphia, Pa.), W. Sawicki and P. Koldovsky. *J Nat Cancer Inst* 46(6):1317-1322, 1971

Antisera against 1-celled unfertilized mouse eggs (AE serum) was found to be cytotoxic for SV40-transformed mouse fibroblasts at dilutions of 1:96 and for adenovirus- and polyoma virus-transformed cells at dilutions of 1:12. AE serum was not cytotoxic for SV40-transformed cells of species other than the mouse. Absorption of AE serum with mouse cells transformed by SV40 abolished the cytotoxicity of the serum against mouse eggs; absorption of the serum with cells transformed by other viruses did not affect the cytotoxicity of the AE serum for mouse egg cells. Antiserum against SV40-transformed mouse fibroblasts was cytotoxic for mouse eggs and for untransformed mouse fibroblasts. Sera against normal mouse spleen cells were cytotoxic for spleen cells and for SV40-transformed mouse fibroblasts only. When spleen cells were absorbed with antiserum to SV40-transformed mouse fibroblasts, the cytotoxicity of the serum for spleen cells was abolished but the cytotoxicity of the serum for SV40-transformed mouse fibroblasts was not affected.

0166 COMPLEMENT FIXATION WITH A SOLUBLE ANTIGEN: CONSIDERABLE DIFFERENCES BETWEEN SERA FROM PATIENTS WITH BURKITT'S LYMPHOMA, WITH RHINOPHARYNGEAL CANCER OR WITH INFECTIOUS MONONUCLEOSIS. (Fr.) Sohier, R. (Int. Ctr. Cancer Res., Lyon, France) and G. De-The. *CR Acad Sci (D)* 273(1):121-124, 1971.

Tests were carried out on sera from patients with rhinopharyngeal cancer, Burkitt's lymphoma, infectious mononucleosis, and normal subjects, using a "soluble" antigen prepared from the Pope line of leukemic cells. The tests included both immunofluorescence and complement fixation with the "soluble" antigen. The results revealed a highly positive reaction to both tests in the sera of patients with cancer of the rhinopharynx. There was no agreement

however for the other 3 groups of subjects; disagreement was highest in patients with Burkitt's lymphoma (positive with immunofluorescence, completely negative with complement fixation). In patients with infectious mononucleosis, 44 of 94 sera were positive with immunofluorescence and only 4 were positive with the complement fixation test. In the normals, out of 73 positive reactions with immunofluorescence, 34 showed a positive reaction with the complement fixation test. The differences in immunological response could be due either to the immunological character of the virus, the nature of the lymphatic lesions, or the response of the host.

0167 IMMUNOLOGICAL REACTIVITY OF MICE INJECTED WITH LEUKAEMIC CELLS. (E.) Hrsak, I. (Inst. Rudjer Boskovic, Zagreb, Yugoslavia). *Advances Exp Med Biol* 12:533-538, 1971.

0168 IMMUNIZATION WITH IRRADIATED TUMOUR CELLS AND SPECIFIC LYMPHOCYTE CYTOTOXICITY IN MALIGNANT MELANOMA. (E.) Currie, G. A. (Chester Beatty Res. Inst., Surrey, England), F. Lejeune and G. H. Fairley. *Brit Med J* 2(5757):305-310, 1971.

0169 ANALYSIS OF THE IMMUNOSUPPRESSIVE AND ONCOGENIC EFFECTS OF HETEROLOGOUS ANTI-LYMPHOCYTE SERUM. (E.) Zipp, P. (U. California Med. Ctr., San Francisco) and S. L. Kountz. *Amer J Surg* 122(2):204-208, 1971.

0170 STUDIES ON A CRYSTALLINE MYELOMA PROTEIN. (E.) Leikola, J. (Dept. Med., U. California, San Francisco), H. H. Fudenberg and S. B. Smith. *Immunochemistry* 8(6):559-562, 1971.

0171 HEAVY-LIGHT CHAIN DISULPHIDE BRIDGE COMMON TO  $\gamma$ A1 AND A GENETIC VARIANT OF  $\gamma$ A2 IMMUNOGLOBULINS. (E.) Mihaescon, E. (Hosp. St. Louis, Paris, France), M. Seligman and B. Frangione. *Nature* 232(33):220-221, 1971.

0172 IMMUNIZATION OF RATS AGAINST THE YOSHIDA ASCITES HEPATOMA WITH VIABLE CELLS INJECTED SUBCUTANEOUSLY OR INTRAMUSCULARLY. (E.) Bellelli, L. (Regina Elena Inst. Cancer Res., Rome, Italy), A. Nista and M. L. Sezzi. *Oncology* 25(3):249-257, 1971.

0173 IMMUNOLOGIC RESPONSE OF AKR MICE IN DIFFERENT PHASES OF DEVELOPMENT OF TRANSPLANTED GROSS LEUKEMIA: II. COMPARATIVE INVESTIGATION OF CELLULAR AND HUMORAL ANTIBODY FORMATION. (E.) Golubska, B. (Med. Sch., Wroclaw, Poland), H. Szalaty, A. Stelmachowska and Z. Skurska. *Arch Immunol Therap Exp* 19(3):369-376, 1971.

0174 SUBFRACTIONS OF  $\gamma$ G-MYELOMA GLOBULINS BY HYDROXY-APATITE COLUMN CHROMATOGRAPHY. (E.) Roelcke, D. (Inst. Immunol. Serol., U. Heidelberg, Germany) and H. Jungfer. *German Med* (1):7-8, 1971.

0175 SEARCH FOR GROUP-SPECIFIC ANTIBODIES OF AVIAN LEUKOSIS VIRUS IN HUMAN LEUKEMIC SERA. (E.) Roth, F. K. (Dept. Microbiol., State U. New York, Syracuse) and R. M. Dougherty. *J Nat Cancer Inst* 46(6):1357-1359, 1971.

0176 STRUCTURAL CHARACTERIZATION OF A HUMAN MONOCLONAL IgA PROTEIN. (E.) Parkhouse, R. M. E. (Natl. Inst. Med. Res., London, England), G. Virella and R. R. Dourmashkin. *Clin Exp Immunol* 8(4):581-591, 1971.

0177 FACIAL TUMOUR ASSOCIATED WITH MONOCLONAL IgA DISEASE WITH  $\mu$  CHAIN FRAGMENT. (E.) Price, E. (State U. New York, Downstate Med. Ctr., Brooklyn, N.Y.), L. Biro, A. Josephson and A. Nicastri. *Brit J Derm* 84(6):534-538, 1971.

0178 INDUCED OPTICAL ACTIVITY OF 2,4-DINITRO-PHENYL-LYSINE SPECIFICALLY BOUND TO MOUSE MOPC-315 MYELOMA PROTEIN. (E.) Rockey, J. M. (Med. Sch., Cambridge, England), K. J. Dorrington and P. C. Montgomery. *Nature* 232(5307):192-194, 1971.

0179 POSSIBLE EXPLANATION FOR LOSS OF DETECTABLE ANTIBODY IN PATIENTS WITH DISSEMINATED MALIGNANT MELANOMA. (E.) Lewis, M. G. (Memorial U., St. Johns, Newfoundland, Canada), T. M. Phillips, K. B. Cook. *Nature* 232(5305):52-54, 1971.

0180 RATE OF SOMATIC MUTATION IN IMMUNOGLOBULIN PRODUCTION BY MOUSE MYELOMA CELLS. (E.) Coffino, P. (Albert Einstein Coll. Med., Bronx, N. Y.) and M. D. Scharff. *Proc Nat Acad Sci USA* 68(1):219-223, 1971.

0181 TRANSPLANTATION OF HUMAN TUMORS INTO THE CHEECK POUCH OF NEONATALLY THYMECTOMIZED GOLDEN HAMSTERS. (Ger.) Dehlinger, H. (Med. Clin., U. Erlangen, Germany) and S. Witte. *Z Krebsforsch* 76(1):65-68, 1971.

#### See also:

- \* (Rev): 0001, 0007, 0008, 0009, 0010, 0011, 0013, 0016, 0021, 0024, 0025, 0030
- \* (Phys): 0101
- \* (Viral): 0110, 0111, 0134, 0135



- 0182 MARROW CHROMOSOME STUDIES IN "PRELEUKEMIA": FURTHER CORRELATION WITH CLINICAL COURSE. (E.) Nowell, P. C. (Sch. Med., U. Pennsylvania, Philadelphia). *Cancer* 28(2):513-518, 1971.

Bone marrow cells from 26 patients with myeloproliferative diseases, 16 patients with pancytopenia and 9 patients with miscellaneous blood conditions were examined for chromosomal aberrations. Eleven of the 26 patients with myeloproliferative conditions showed clonal chromosomal abnormalities (3 of these patients had been treated with  $^{32}\text{P}$  radiation); 5 of the pancytopenia patients showed abnormalities and none of the miscellaneous blood condition patients showed abnormalities. Of the 16 patients with chromosomal aberrations, 9 developed acute or subacute leukemia within 3 months of manifesting chromosomal abnormalities. None of the 3 patients treated with  $^{32}\text{P}$  and showing chromosomal aberrations developed leukemia; aberrations in these cases may have been produced by the radiation. Four patients without chromosomal aberrations in the myeloproliferative and pancytopenia groups developed frank leukemia. Although no particular type of aberration was noticeably associated with leukemic development, it was concluded that patients who have not received radiation therapy but who have developed marrow chromosome aberrations are likely to develop leukemia.

- 0183 LUNG CARCINOMA OF SHEEP (JAAGSIEKTE): II. HISTOGENESIS OF THE TUMOR. (E.) Perk, K. (Hebrew U. Jerusalem, Rehovot, Israel), I. Hod, B. Presentey and T. A. Nobel. *J Nat Cancer Inst* 47(1):197-200, 1971.

Pulmonary tumor material was prepared for electron microscopic examination from 9 Awassi sheep in which Jaagsiekte had been histologically and clinically diagnosed. Tumor nodes were found in the lungs of diseased animals, and the pathological pattern of lung tissue varied in different areas of the lung. Near tumor nodules, solitary or small rows of neoplastic cells were seen; these cells apparently derived from type B alveolar epithelial cells. Neoplastic cells contained glycogen granules while normal cells did not. At the margins of tumor nodules, alveoli were lined by a single layer of epithelium, and epithelial cells were well differentiated and cuboidal or columnar in shape. Some alveoli in these regions were filled with deciduous neoplastic cells devoid of glycogen. Central areas of tumor nodules showed intensely proliferated cords, sheets or nests of anaplastic epithelial cells. Proliferative cells contained scanty cytoplasm and had large nuclei and nucleoli. In deep regions of extensive tumor nodes, the usual sarcomatous cell pattern was further differentiated; here more mature fibroblasts were seen. Some epithelial cells were also seen in these regions. Some epithelial tumor cells contained intracytoplasmic PAS-positive droplets. In impression smears from the cut surface of lung tumors 2 main types of epithelial cells were seen: irregular cuboidal cells and high columnar cells.

- 0184 STROMAL RESPONSE IN BREAST CARCINOMA AND FIBROADENOMATOSIS, ESTIMATED BY THE AID OF THE ALKALINE PHOSPHATASE ACTIVITY. (E.) Jensen, H. (Rigshosp., Copenhagen, Denmark) and T. Schiodt. *Acta Path Microbiol Scand* 79(A):321-329, 1971.

Alkaline phosphatase was assayed in tumor cells and tumor stroma from 40 biopsy specimens of mammary carcinoma; 32 of the cases showed fibroadenomatosis, 7 were fibroadenomas and 1 was carcinoma *in situ*. Seven of the 40 breast carcinomas showed slight to moderate alkaline phosphatase activity in tumor cells, while 33 tumor cell specimens showed no enzyme activity. The stroma around the tumor often showed increased numbers of fibroblasts; these fibroblasts showed pronounced alkaline phosphatase activity. Fibroblastic areas having marked levels of alkaline phosphatase activity in tumor stroma were designated "reaction zones". Reaction zones were present in 65% of the breast carcinomas while 7.5% of carcinomas showed zones which were doubtfully positive for alkaline phosphatase. Anaplastic carcinoma biopsy specimens showed reaction zones more often than did more differentiated carcinoma biopsy specimens; 33% of grade I anaplastic specimens had reaction zones while 90% of grade III anaplastic specimens had reaction zones. Reaction zones were also more frequent in carcinoma biopsy specimens in which there was pronounced lymphocyte infiltration. In 18% of biopsy specimens with fibroadenomatosis stromal reaction zones were found to be of the same appearance as that described for the carcinomas. No reaction zones were found in the stroma of the fibroadenomas; fibroblasts were often abundant in the stroma of fibroadenomas.

- 0185 INHIBITION OF TRANSFORMATION OF MAMMARY PRENEOPLASTIC NODULES TO TUMOR IN C3H MICE FED A PHENYLALANINE-DEFICIENT DIET. (E.) Hui, Y. H. (Cancer Res. Genet. Lab., U. California, Berkeley), K. B. DeOme and G. M. Briggs. *J Nat Cancer Inst* 47(1):245-249, 1971.

Virgin female strain C3H/Crgl mice were fed on phenylalanine (P)-deficient diets for 40 wk; the mice had been given implanted hyperplastic alveolar nodules in the inguinal mammary fat pads 2 wk prior to the start of P-deficient feeding. P levels in the diets of the mice were 0.300%, 0.150%, 0.135%, 0.120% and 0.090%. The progression of hyperplastic alveolar nodules to frank mammary tumors and the time required for this progression were observed in mice on the P-deficient diet. There was a direct correlation between the amount of P in the diet, the capability of nodules to produce tumors, and the latent period; as the amount of dietary P decreased the production of tumors by nodules decreased and the latency increased. In mice given a 0.300% P concentration, 89.7% of nodules produced tumors and the time taken for 50% of nodules to produce tumors (TE50) was 112 days; in mice given a 0.120% concentration of P, 51.4% of nodules produced tumors and the TE50 was 280 days. In mice given a 0.090% concentration of P, 42.4% of nodules developed tumors and the TE50 could not be cal-



culated since tumor formation did not reach 50% in 10 months. Mice fed 0.90% and 0.120% P diets showed poorly developed mammary glands and atrophic ovaries with the corpora lutea almost lacking. Mice given higher concentrations of P had well-developed mammary glands and these mice also had normal ovaries with many corpora lutea.

- 0186 A STUDY OF CARCINOMA OF UTERINE CERVIX WITH SPECIAL REFERENCE TO ITS CAUSATION AND PREVENTION. (E.) Malhotra, S. L. (Med. Dept., South-eastern Railway, Calcutta, India). *Brit J Cancer* 25(1): 62-71, 1971.

In a survey of 50 cases of cervical carcinoma conducted in Calcutta a correlation was found between frequency of sexual intercourse and incidence of cervical cancer. Patients were diagnosed as having cervical adenocarcinoma in 1 case, squamous cell carcinoma in 48 cases and undifferentiated carcinoma in 1 case. Patients were generally of low socio-economic status (94% had a monthly income of \$55.00 or less). In a comparison of cervical cancer patients and age-matched healthy controls no significant differences were found in penile hygiene measures taken by the male consort of subjects in the 2 groups. However, carcinoma patients reported having sexual intercourse 12.43 (mean) times/month, while healthy controls reported having sexual intercourse 3.92 (mean) times/month. In an attempt to determine the cause of this correlation of frequency of sexual intercourse with cervical cancer the pH of seminal fluid from males ejaculating daily, weekly and fortnightly was determined. It was found that as frequency of ejaculation increased the semen became more alkaline. It was known that an alkaline milieu surrounding mucus-producing cells such as those in the cervix dissolves the mucus which then escapes from the cell; this in turn causes hyperplasia, metaplasia and an increase in mitotic activity. It was suggested that it is the alkaline reaction of semen and mucus-producing cervical cells which accounts for the observed correlation between frequency of sexual intercourse and cervical carcinoma incidence.

- 0187 ARGINASE AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITIES IN SPONTANEOUS MAMMARY CARCINOGENESIS. (E.) Bhide, S. V. (Tata Mem. Ctr., Bombay, India). *Brit J Cancer* 25(1):182-185, 1971.

Arginase and glucose-6-phosphate dehydrogenase activity were assayed in mammary tissue from tumor-free C3H Jax virgin mice of different ages and in precancerous mammary nodules and mammary tumors developed by mice of the same strain. Mice were examined for enzyme activity at 4-, 8-, and 12-months-old. Levels of arginase and glucose-6-phosphate dehydrogenase activity were similar in tumor-free mice in the 3 age-groups tested; arginase activity in mice in these age-groups ranged from 0.29-0.3  $\mu\text{g}$  urea formed/hr/ $\mu\text{g}$  protein and glucose-6-phosphate dehydrogenase activity in the

3 age-groups ranged from 0.36-0.42 (expressed in terms of optical density at 3600  $\text{\AA}$ /min/ $\mu\text{g}$  protein). Arginase activity in precancerous nodules was 1.4  $\mu\text{g}$  urea formed/hr/ $\mu\text{g}$  protein and glucose-6-phosphate dehydrogenase activity in precancerous nodules was 0.6 (changes in optical density at 3600  $\text{\AA}$ /min/ $\mu\text{g}$  protein). Arginase activity in tissue from mammary tumors was 1.93  $\mu\text{g}$  urea formed/hr/ $\mu\text{g}$  protein and glucose-6-phosphate dehydrogenase activity in tumor tissue was 0.67.

- 0188 THE EARLY NATURAL HISTORY OF MURINE GERMINAL TESTICULAR TUMORS. (E).

Mount, B. M. (Mem. Hosp. Cancer Allied Dis., New York, N.Y.) and L. C. Stevens. *J Urol* 105(6):812-816, 1971.

The development of spontaneous testicular tumors (teratomas) and of teratomas induced by engrafting genital ridges from mouse embryos into mouse testicles, was observed microscopically in strain 129/Sv-CPS1J mice. Both types of tumor development were similar. Tumors appeared initially as intratubular clumps of basophilic undifferentiated embryonal carcinoma cells. The tumors grew, bursting the tubules and rapidly enlarging. Fifty-nine percent of spontaneous tumors were multifocal and 80% of induced tumors were multifocal. In multifocal tumors, more than 1 tumor focus was often found in the same tubule; foci were frequently in close proximity. It was thought that adjacent tumor foci were derived from a single primordial neoplastic cell.

- 0189 GASTRIC CARCINOMA: HISTOMORPHOLOGY OF SAMPLES FROM DIFFERENT REGIONS OF THE GASTRIC MUCOSA. (Ger.) Krentz, K. (Aachen Hosp., Germany) *Med Klin* 66(25):920-923, 1971.

Target biopsies were carried out in 105 patients with gastric carcinoma. Specimens were taken from tumor, tumor-adjacent and tumor-distal portions of the gastric mucosa. The mucosa from the tumor-adjacent portions revealed atrophic alterations in 90 patients; there was no correlation between the alterations and the site of the gastric tumor. Goblet cell metaplasia of the mucosa was seen in 66 of the 90 patients; it occurred near the tumors. The mucosal specimens from the distal portions of the tumor revealed atrophic alterations with or without goblet cell metaplasia in 61 patients. The patients with a histologically normal mucosa of the gastric body had developed carcinoma in the antral region. Gastric chromoscopy showed that cancer developed in portions of the gastric mucosa where complete failure of the acid secretory function occurred.

- 0190 DIFFERENTIAL RESPONSE OF RIBONUCLEIC ACID POLYMERASE IN PRENEOPLASTIC AND NEOPLASTIC OVARIES OF MICE FOLLOWING OESTRADIOL TREATMENT. (E.) Bruzzone, S. (Fac. Med., U. Chile, Santiago). *Brit J Cancer* 25(1):158-165, 1971.

Virgin female mice of the C57BL/6 strain were given intrasplenic ovarian grafts when 2-months-old and RNA polymerase was determined in the nuclear fraction of normal ovaries, 60-day-old preneoplastic intrasplenic ovarian grafts, and ovarian tumors after 7 months of ovary grafting into the spleen. In preneoplastic grafts, RNA polymerase activity corresponded to that of normal ovaries, while in ovarian tumors, the enzyme value was 2-3 times higher. Estradiol injected s.c. in amounts of 10 µg for 10 days acted as a depressant of the host pituitary gonadotrophic potency, decreasing the enzyme level in the grafts; no change was observed in similarly treated tumors. It is believed that hormonal mechanisms regulating the genetic nuclear expression are operating only in the 2-month-old preneoplastic ovarian cell, while autonomy from these regulating mechanisms is achieved by 7-month-old tumor cells.

0191 THE ORIGIN OF RETICULUM CELL SARCOMA IN CHRONIC OSTEOMYELITIS OF THE MANDIBLE.

(E.) Hornova, J. (Med. Fac., J. E. Purkyne U. Brno, Czechoslovakia) and M. Machalka. *Scripta Med* 44(2-3):101-109, 1971.

0192 ULTRASTRUCTURAL STUDY OF BASAL CELL CARCINOMA AND ITS VARIANTS WITH COMMENTS ON HISTOGENESIS.

(E.) Reidbord, H. E. (Shadyside Hosp., Pittsburgh, Pa.), H. L. Wechsler and E. R. Fisher. *Arch Derm* 104:132-140, 1971.

0193 DEVELOPMENT OF MALIGNANT LYMPHOMA DURING THE COURSE OF ADULT CELIAC DISEASE: A CLINICOPATHOLOGIC STUDY OF A 49-YEAR OLD MALE VETERAN.

(E.) Ansari, A. (Minneapolis VA Hosp., Minneapolis, Minn.) and S. E. Silvis. *Amer J Gastroent* 55(5):482-488, 1971.

0194 PATHOMECHANISM OF INCREASED RES ACTIVITY IN RATS BEARING YOSHIDA SARCOMA. (E.)

Lazar, G. (Med. U. Szeged, Szeged, Hungary) and E. Husztik. *Advances Exp Med* 15:401-406, 1971.

0195 THE RATIONALE OF PRACTICE FOR POLYPOID LESIONS OF THE COLON. (E.)

Spratt, J. S. (Cancer Res. Ctr., Columbia, Mo.) and F. R. Watson. *Cancer* 28(1):153-159, 1971.

0196 MALIGNANCY IN INFLAMMATORY DISEASE OF THE LARGE INTESTINE. (E.)

Morgan, C. N. (St. Mark's Hosp., London, England). *Cancer* 28(1):41-44, 1971.

0197 THE COLONIC PERICRYPTAL FIBROBLAST SHEATH: REPLICATION, MIGRATION AND CYTODIFFERENTIATION OF A MESENCHYMAL CELL SYSTEM IN ADULT TISSUE

III. REPLICATION AND DIFFERENTIATION IN HUMAN HYPERPLASTIC AND ADENOMATOUS POLYPS. (E.) Kaye, G. I. (Coll. Phys. Surg., Columbia U., New York, N. Y.), R. R. Pascal and N. Lane. *Gastroenterology* 60(4):515-536, 1971.

See also:

- \* (Rev): 0014, 0023
- \* (Chem): 0060, 0063
- \* (Phys): 0101



198 INCIDENCE OF AND MORTALITY FROM MALIGNANT MELANOMA BY ANATOMICAL SITE. (E.) Lee, J. H. (Sch. Pub. Hlth., U. Washington, Seattle) and . Yongchaiyudha. *J Nat Cancer Inst* 47(1):253-263, 1971.

The incidence among males and females of malignant melanoma of various sites was determined from figures compiled by the National Cancer Registration Scheme of England and Wales between 1962-1967. Incidence and mortality rates for malignant melanoma for all sites in England and Wales increased with age among younger males and females; the female incidence rate was generally higher than the male incidence rate, while male and female mortality rates coincided. Among females aged 45-59-yr-old there were 1,049 cases of malignant melanoma while among males in this group there were 526 cases of melanoma. The incidence of malignant melanoma in both sexes was maximal in this age group; in older groups, malignant melanoma incidence decreased. Incidence and mortality from malignant melanoma of the head and neck were low in persons under 45-yr-old but both incidence rates and death rates for melanoma of this site increased sharply in persons over 45-yr-old. Male and female incidence and death rates for malignant melanoma of the head and neck were similar in all age groups. Incidence rates and death rates for malignant melanoma of the trunk rose with advancing age; however, the incidence of melanoma at this site was never high. Low incidence of melanoma on the trunk may have been due to the fact that this region is usually covered by clothing. Malignant melanoma of the upper limb showed a similar pattern of incidence and mortality to that of melanoma of the trunk; in neither case was there a sharp increase in incidence among the elderly. While the incidence of malignant melanoma of the lower limb increased steadily with age among males, among females incidence of melanoma of this area dropped after age 40-yr-old. Females under 70-yr-old had a higher incidence of malignant melanoma of the lower limb than males. It was thought that sunlight exposure might be associated with the difference in the incidence patterns between the sexes of melanoma of the lower limb.

199 CHRONIC GASTRITIS IN JAPANESE WITH REFERENCE TO HIGH INCIDENCE OF GASTRIC CARCINOMA. (E.) Imai, T. (Fac. Med., Kyushu U., Fukuoka, Japan), T. Kubo and H. Watanabe. *J Nat Cancer Inst* 47(1):179-191, 1971.

The antral mucosa and body mucosa from the stomachs of 360 apparently healthy Americans were examined for gastritis and the incidence of gastritis was compared with that found in 260 stomachs of apparently healthy Japanese. Japanese were known to have a high incidence of stomach carcinoma, and Americans a low incidence of this condition. The incidence of antral mucosa gastritis was found to increase with the age of the subject; Japanese stomach antral mucosa showed a higher incidence of gastritis than did American stomach antral mucosa. The percentage of chronic antral gastritis among Japanese aged 11-20-yr-old was 36.8% and the percentage among Jap-

anese aged 61-70-yr-old was 86.4%. In contrast, the percentage of antral gastritis among Americans in the second decade of life was 6.7% and the percentage of gastritis among Americans in the seventh decade of life was 37.3%. In all Japanese specimens with gastritis, parenchymal changes were seen. Gastritis of body mucosa was more common among older subjects than among younger subjects, and further, was more common among Japanese than among Americans. The incidence of gastritis was also investigated in stomach tissue taken from American and Japanese patients with gastric carcinoma, gastric ulcer and duodenal ulcer. Gastritis was more common in these subjects than in stomachs from healthy subjects. Intestinal parenchymal metaplasia was more common among older patients in stomach material taken from patients with stomach lesions. Metaplasia was also found to be more common among Japanese than among Americans.

0200 REVERSE SMOKING IN ANDHRA PRADESH, INDIA: A STUDY OF PALATAL LESIONS AMONG 10,169 VILLAGERS. (E.) Pindborg, J. J. (Tata Inst. Fundamental Res., Bombay, India), F. S. Mehta, P. C. Gupta, D. K. Daftary and C. J. Smith. *Brit J Cancer* 25(1):10-20, 1971.

A survey of 10,169 villagers was conducted in the Srikakulam district in Andhra Pradesh, South India to determine the correlation of palatal neoplastic lesions with tobacco use; special attention was given to the habit of reverse smoking, in which a rolled tobacco leaf is smoked with the lighted end placed in the mouth. Seventy-four percent of villagers were found to use tobacco in some form and 43.8% were found to be reverse smokers. Females practiced reverse smoking more than males; the female:male ratio for the habit was 1.7:1. Reverse smoking was especially widespread among females aged 55-64-yr-old (75% of women in this age group were reverse smokers). Other tobacco habits included conventional smoking and tobacco chewing. Ten cases of oral cancer were found in the population studied; the prevalences of preleukoplakia, leukoplakia and leukokeratosis nicotina palati were, resp., 2.9%, 4.9% and 9.5%. Eighty-three percent of persons with leukoplakia were reverse smokers and 91.7% of persons with palatal leukoplakia were reverse smokers. While 8.8% of reverse smokers had leukoplakia, only 0.1% of tobacco non-users had leukoplakia. Preleukoplakia showed a correlation with tobacco use similar to that shown by leukoplakia. Eighty-seven percent of persons with leukokeratosis nicotina palati were reverse smokers. All palatal lesions showed a female predominance and an increasing prevalence with advancing age. The percentage of persons with oral cancer who were reverse smokers was 0.2% and the percentage of oral cancer victims who smoked and chewed tobacco was 0.1%. None of the persons who did not use tobacco had oral cancer. Eighty percent of palatal biopsies taken showed hyperorthokeratosis. Epithelial atypia were found in 15.3% of leukoplakias, in 3.6% of preleukoplakias and in 9.1% of leukokeratosis nicotina palati cases.

- 0201 BURKITT'S LYMPHOMA IN ILESHA, WESTERN NIGERIA. (E.) Mulligan, T. O. (Wesley Guild Hosp., Ilesha, Western Nigeria). *Brit J Cancer* 25(1):53-61, 1971.

The incidence and population distribution of Burkitt's lymphoma was investigated in a series of 65 cases recorded in the town of Ilesha in Western Nigeria between 1954 and 1969. Forty-five percent of cases involved the maxilla as main site, 35% involved the abdominal mass and 18% involved the orbit. There were 41 male cases and 23 female cases (sex was unknown in 1 case); the excess of male cases was confined to cases involving facial lesions. More than half the total number of cases involved persons aged 5-9-yr-old; of 27 jaw and orbital tumors 22 appeared in persons under 8-yr-old. No unexpected excess of Burkitt's lymphoma was found in any distinct ethnic group (however, 95% of patients examined were of the Yoruba tribe). Annual age-specific incidence rates were calculated for Burkitt's lymphoma among the Ileshi townsmen; the incidence/100,000 population/yr was 0.6 among persons aged 0-4-yr-old, 4.4 among persons aged 5-9-yr-old, and 1.8 among persons aged 10-14-yr-old. Community immunization programs directed against malaria and other diseases may account for the differing incidence rates of Burkitt's lymphoma observed in western Nigeria.

- 0202 GEOGRAPHICAL DISTRIBUTION OF BURKITT'S LYMPHOMA IN THE DEMOCRATIC REPUBLIC OF THE CONGO. (E.) Jain, A. C. (U. Clin., U. Louvain, Kinshasa, Congo), A. M. Renoirte and A. Schroder. *W Afr Med J* 20(3):247-249, 1971.

Twelve cases of Burkitt's lymphoma seen between 1963 and 1968 at a hospital in the Congo Centrale area of the Republic of the Congo were described together with a theory for the etiology of this condition. According to this theory, 2 factors work to cause Burkitt's lymphoma in a population: a vectored parasite, probably malaria, which alters the reticuloendothelial system of the host, and a virus such as Epstein-Barr virus. Epstein-Barr virus has been found in as many as 65% of a group of Congolese children. In addition, areas of high malaria incidence in the Congo appear to be areas of high Burkitt's lymphoma incidence (e.g. parts of the Congo Centrale area.)

- 0203 EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION OF CANCER IN AFRICA. (Fr.) Quenum, C. (No affiliation), R. Camain and R. Baylet. *Med Afrique Noire* 18(3):165-188, 1971.

The incidence and distribution of cancer in Africa are reviewed with tabulation of data as to age, sex, geographic area, localization in the body and comparative data with other non-African countries. Etiological factors seem to be related to the environment. Hereditary differences are explained by sociocultural rather than by genetic factors. The genetic factor, which is difficult to evaluate

in man, may play a role in the determination of the threshold of intervention of the extra-genetic factors. An analysis of numerous etiological factors attributed to the development of cancer could not establish any single factor responsible for a particular form of cancer.

- 0204 BREAST CANCER AMONG WOMEN IN SENEGAL. (Fr.) Menye, P. A. (Cancer Res. Institut, Dakar, Senegal), Y. Pouliguen and D. Simaga. *Med Afrique Noire* 18(4):369-379, 1971.

A report on 260 cases of mammary cancer in Senegal is presented. These cases represent 20% of all the 1267 malignant tumor cases seen in the Cancer Institute in Dakar, treated over a period of 10 years. Statistical results show that the appearance of breast cancer in the female in Senegal occurs earlier than in other countries; that a maximum incidence occurs at the ages between 40 and 60 years; and that in spite of the finding that most of the patients came from rural areas, none of the endemic disease in Senegal had any particular effect upon the development of breast cancer. Diet, which in Africa is low in protein and high in lipids and in carbohydrates, was not instrumental in the development of hepatic lesions in these patients.

- 0205 THE EPIDEMIOLOGY OF MAMMARY CANCER. (It.) Cappa, A. P. M. (Piemonte and Valle d'Aosta Tumor Reg., Torino, Italy), E. Anglesio, M. Panero, G. Bonelli. *Minerva Ginec* 23(7):320-336, 1971.

The Piemontese tumor registry office recorded 33,963 malignant tumors for the period 1965-1968 in the region of Piedmont (N. Italy), an area of approximately 4,000,000 population. Of these, 4,617 were mammary tumors that constituted 26% of the total malignancies in female and 0.5% of the malignancies in male patients. The highest incidence of mammary tumors was found in women between 30-60 yr-of-age with a considerable prevalence in nulliparous women during the post menopausal stage. An analysis of methods to be used in tumor epidemiology and a review of the world distribution of mammary cancer are presented.

- 0206 UTERINE MALIGNANCIES OF UNSPECIFIED ORIGIN. (E.) Schoenberg, B. S. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.) and J. C. Bailar, III. *Arch Environ Health* 23(1):77-81, 1971.

Records of 3,775 deaths in the United States from cancer of the uterus were reviewed to determine the precise site of the fatal lesion. Of these cases, 729 were determined to be cases of cancer of the cervix uteri and 1,718 were determined to be cases of cancer of the uterine corpus. The reassignment of cases initially registered simply as "uterine cancer" did not affect age-specific mortality rates for cervical and uterine cancer among younger women. Rates for cancer of the cervix uteri among



women aged 60-yr-old and older, however, were increased by the addition of cervix uteri cases originally recorded simply as cases of uterine cancer.

# 0207 CANCER OF THE SKIN. AN ANALYTICAL AND EPIDEMIOLOGICAL STUDY OF 454 CASES.

(Sp.) Aceves-Ortega, R. (Guadalajara U., Mexico). *Dermatologia* 14(3):354-376, 1970.

Skin neoplasia constituted 2.27% of the dermatological diseases encountered at the medical school clinics in Guadalajara. The major part of the patient population (75%) was from the states of Jalisco and Michoacan and the highest incidence in skin neoplasia was found to be confined to the 50-80-yr-old female population. The central facial region appeared to be the main site of the neoplastic lesions. Basal cell epithelioma constituted 74%, squamous cell epithelioma constituted 20% and malignant melanoma constituted 3% of all the skin tumors. Bowen's and Paget's disease appeared to be rare. Reference is made to certain relationships found between climatic conditions (sunlight exposure), skin pigmentation and economical status and incidence of skin neoplasia for the given geographical region.

# 0208 ESOPHAGEAL CANCER IN A MIDWESTERN COMMUNITY. (E.) Lynch, H. T. (Omaha, Neb.), D. D. Ewers, A. J. Krush, E. A. Sharp and M. J. Swartz. *Amer J Gastroent* 55(5):437-442, 1971.

A survey of the Omaha-Douglas County, Nebraska, area revealed 16 cases of esophageal cancer (13 males). The patient had died in all cases, the age at death ranging from 52-90-yr-old. All patients were from a low socio-economic level, and 11 of the patients were alcoholics. Four patients worked in the meat-packing industry and 1 had been exposed to animals in zoos. Fourteen of the patients had squamous cell carcinoma of the esophagus, while 2 had anaplastic carcinoma. The finding of 16 cases of esophageal carcinoma in the course of 1 yr in the Omaha area yielded an incidence rate of 4.6 cases/100,000 population for this disease in this region; the incidence rate for esophageal cancer in the Omaha area was significantly higher than that in the United States as a whole.

# 0209 RELATION OF GASTROINTESTINAL CANCER MORTALITY TO CANCER MORTALITY IN GENERAL. (E.) Gregor, O. (U. Hosp., Charles U., Prague, Czechoslovakia), R. Toman and F. Prusova. *Scand J Gastroent* 6(9):79-85, 1971.

# 0210 COMPLETENESS AND RELIABILITY OF LUNG CANCER REGISTRATION IN THE SWEDISH CANCER REGISTRY. (E.) Larsson, S. (Sahlgren's Hosp., U. Gothenburg, Gothenburg, Sweden). *Acta Path Microbiol Scand* 79A(A):387-398, 1971.

# 0211 GEOGRAPHICAL VARIATION OF CARCINOMA OF THE PENIS IN UGANDA. (E.) Schmauz, R. (Med. Sch., Makerere U., Kampala, Uganda) and D. K. Jain. *Brit J Cancer* 25(1):25-32, 1971.

# 0212 PITUITARY TUMOURS IN UGANDA. (E.) Bailey, I. C. (Mulago Hosp., Kampala, Uganda) and J. D. Thomas. *East Afr Med J* 48(3):90-99, 1971.

# 0213 THE INCIDENCE OF SKIN CANCER IN SOUTHERN ARIZONA (TUCSON). (E.) Schreiber, M. M. (Coll. Med., U. Arizona, Tucson), S. I. Shapiro, C. Z. Berry, R. F. Dahlen and R. P. Friedman. *Arch Derm* 104:124-127, 1971.

# 0214 THE 30-YEAR TREND OF BRONCHOGENIC CARCINOMA IN OLMSTEAD COUNTY, MINNESOTA, 1935-1964. (E.) Byrd, R. B. (Mayo Grad. Sch. Med., Rochester, Minn.), F. T. Nobrega, M. B. Divertie, D. T. Carr, L. B. Woolner and L. T. Kurland. *J Chronic Dis* 24:9-18, 1971.

# 0215 POPULATION STUDIES OF BONE TUMOURS. (E.) Sissons, H. A. (Royal Natl. Orthopedic Hosp., London, England). *Proc Roy Soc Med* 64(6):643-644, 1971.

# 0216 RELATIONSHIP OF HERPES SIMPLEX GENITAL INFECTION AND CARCINOMA OF THE CERVIX: POPULATION STUDIES. (E.) Centifanto, Y. M. (Coll. Med., U. Florida, Gainesville), R. J. Hildebrandt, B. Held and H. E. Kaufman. *Amer J Obstet Gynec* 110(5):690-692, 1971.

# 0217 A REVIEW OF GASTRO-DUODENAL PATHOLOGY IN BUGOSA DISTRICT, UGANDA. (E.) Hancock, B. D. (Manchester Royal Infirm., Manchester, England). *East Afr Med J* 48(3):103-108, 1971.

# 0218 REGIONAL VARIATIONS IN PRIMARY LIVER CANCER IN IVORY COAST. (E.) Tuyns, A. J. (Internatl. Agency Res. Cancer, Lyon, France), R. Loubiere and Fr. Duvernet-Battesti. *J Nat Cancer Inst* 47(1):131-135, 1971.

# 0219 CANCER OF THE PANCREAS IN CALIFORNIA, 1942-1967: THE CALIFORNIA TUMOR REGISTRY EXPERIENCE. (E.) Krain, L. S. (Los Angeles, Calif.). *Calif Med* 115(1):38-41, 1971.

0220      CANCER IN IRAN: MALIGNANT TUMORS OF THE  
FEMALE GENITALIA. (E.) Habibi, A. (Dept.  
Path., Tehran U., Tehran, Iran). *Int J Surg* 56(1):  
13-17, 1971.

0222      MALIGNANT NEOPLASMS ACCORDING TO SITE,  
BY SEX AND AGE: MORBIDITY STATISTICS.  
(E.) Anon. *World Health Statistics Report* 24(2):78-  
81, 1971.

0221      AN EPIDEMIOLOGICAL ANALYSIS OF CANCER  
VACCINES. (E). Higginson, J. (Int. Agency  
Res. Cancer, Lyons, France), G. DeThe, A. Geser and  
N. Day. *Int J Cancer* 7(3):565-574, 1971.

See also:

- \* (Rev): 0005, 0006, 0024
- \* (Chem): 0091
- \* (Phys): 0102



# MISCELLANEOUS

223 THE TEMPLATE ACTIVITIES OF NUCLEAR RNAS FROM RAT LIVER, REGENERATING LIVER AND HEPATOMA AH-130 CELLS. (E.) Amano, M. (Natl. Cancer Ctr. Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan) and T. Akino. *J Biochem* 69(4):671-676, 1971.

Nuclear RNAs were prepared from cytoplasm-free nuclei of normal rat liver cells, liver cells from partially hepatectomized rats (livers had been allowed to regenerate for 16 hr) and rat hepatoma cells. The ability of liver cell nuclei from these sources to stimulate amino acid incorporation into protein was studied using a protein synthesizing system with S30 fractions from *Escherichia coli*. The RNA/DNA ratios of cell nuclei from normal liver, regenerating liver, and hepatoma were determined and it was found that normal liver cell nuclei had an RNA/DNA ratio of 0.16 whereas regenerating liver cell nuclei had a ratio of 0.26 and hepatoma cell nuclei a ratio of 0.35. Template activity of nuclear RNAs were expressed in cpm of incorporation of  $^{14}\text{C}$ -leucine by the addition of 100  $\mu\text{g}$  RNA. Normal liver cell nuclei, in 6 separate experiments, showed protein template activities ranging from 60-8260 cpm/100  $\mu\text{g}$  RNA; regenerating liver cell nuclei, in 4 experiments, showed template activities ranging from 4930-6805 cpm/100  $\mu\text{g}$  RNA and hepatoma cell nuclei showed template activities ranging from 2461-3760 cpm/100  $\mu\text{g}$  RNA. In all nuclear RNAs from the 3 cell types, the highest template activity was found in the rapidly sedimenting 35S and 45S RNA regions; no activity was found in low molecular weight RNAs. In normal liver cells, the RNA molecular species which had the capacity for stimulating  $^{14}\text{C}$ -leucine incorporation in nuclear RNA was maximal in the 35S region, while in hepatoma cells RNA molecular species which stimulated leucine incorporation were most highly active in the 35S region.

224 CONTROL OF SOMATIC CELL MITOSIS BY SIMULATED CHANGES IN THE TRANSMEMBRANE POTENTIAL LEVEL. (E.) Cone, C. D., Jr. (Langley Res. Ctr., Natl. Aeronautics and Space Admin., Hampton, Va.) and M. Tongier, Jr. *Oncology* 25(2):138-182, 1971.

Naturally synchronized Chinese hamster cells (CHO cl. line), obtained by shaking off rounded metaphase cells from the surface of large monolayer cell cultures, were used to study the role of the electrical transmembrane potential difference ( $E_m$ ) in the control of somatic cell mitosis. Test media (HEM<sub>100</sub>) were designed to produce intracellular osmotic conditions and concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  approximating those existing at various naturally-generated  $E_m$  levels *in vivo*. Immediate mitotic repression (within 24 hr) occurred in HEM<sub>45</sub> at about -46 mV and complete mitotic arrest was reached in HEM<sub>85</sub> at -75 mV. Reversion to lower  $E_m$  levels resulted in resumption of mitosis even after long term blockage. Mitotic blockage was found to occur in the second half of the  $G_1$  period and to be associated with an arrest of DNA synthesis. Prevention of DNA synthesis was assumed to be due to metabolic or enzymic alterations involving the blockage

of DNA precursor or of polymerase synthesis. Natural variations of the  $E_m$  level of somatic cells seem to constitute an important factor in the control of mitosis *in vivo*.

0225 ABSENCE OF A NATURAL INHIBITOR OF THE tRNA METHYLASES FROM FETAL AND TUMOR TISSUES. (E.) Kerr, S. J. (U. Colorado Med. Ctr., Denver). *Proc Nat Acad Sci USA* 68(2):406-410, 1971

Inhibitors of tRNA methylase were isolated from fetal rabbit liver and from tumor tissue by homogenization, high-speed centrifugation and precipitation at pH 5. The tRNA inhibitor in normal tissue was found to consist of 2 fractions, one having a molecular weight of 75,000-100,000 (the high molecular weight fraction) and the other having a molecular weight of less than 700 (the low molecular weight fraction). The high molecular weight fraction of the tRNA inhibitor was found to be absent in fetal rabbit liver tissue. Tissues from Morris hepatoma 5123 c, Novikoff hepatoma, and Ehrlich ascites tumor cells also lacked the high molecular weight fraction of the tRNA inhibitor; all these tissues had been shown to exhibit elevated tRNA methylase activity.

0226 AUTORADIOGRAPHIC STUDIES OF RNA METABOLISM IN HUMAN LEUKAEMIC BLAST CELLS. (E.) Chan, B. W. B. (Dept. Med., U. Cambridge, England). *Acta Haemat* 45(1):17-22, 1971.

Blood and/or marrow cells from patients with acute myeloid leukemia or acute lymphoblastic leukemia were incubated with  $^3\text{H}$ -uridine and treated with actinomycin D (AMD) in varying amounts; the inhibition of RNA synthesis in the leukemic cells by AMD was measured by the inhibition of the uptake of tritiated uridine by the cells. In one experiment it was found that 0.1  $\mu\text{g}/\text{ml}$  AMD reduced the percentage of  $^3\text{H}$ -uridine-labeled cells to 80% of controls (e.g., leukemic cells incubated with  $^3\text{H}$ -uridine but not treated with AMD) while 1.0  $\mu\text{g}/\text{ml}$  of AMD reduced the percentage of cells incorporating tritiated uridine to 5% of controls. In another experiment, it was found that 2.5 hr after introduction of AMD, cells given 0.4  $\mu\text{g}/\text{ml}$  AMD showed 175% of the initial grain count of  $^3\text{H}$ -uridine-labeled RNA, while cells given 4.0 or 10.0  $\mu\text{g}/\text{ml}$  AMD showed about 25% of the initial grain count. In a third experiment, leukemic cells were incubated for 30 and 180 min with  $^3\text{H}$ -uridine prior to the introduction of 4.0  $\mu\text{g}/\text{ml}$  AMD. Three hr after AMD introduction, cells incubated with  $^3\text{H}$ -uridine for 180 min showed 68% of the initial grain count for labeled RNA while cells incubated for 30 min showed 20% of the initial grain count.

0227 CELL CYCLE CHARACTERISTICS, MATURATION, AND PHAGOCYTOSIS IN VITRO OF BLAST CELLS FROM PATIENTS WITH CHRONIC MYELOCYTIC LEUKEMIA. (E.) Whang-Peng, J. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), S. Perry, T. A. Knutsen and J. J. Gart. *Blood* 38(2):153-161, 1971.

Blood was collected from 7 patients (2 females, 5 males) with chronic myelocytic leukemia; 2 of the patients were in the stable phase of the disease, 1 was in a transitional phase and 4 were in the stage of blastic transformation. Examination of the samples showed a modal chromosome number of 46 in each case and each sample showed the presence of the Ph<sup>1</sup> chromosome. Two stable phase patients and 1 transitional phase patient had only 1 Ph<sup>1</sup> chromosome in their sampled blood cells; 2 blastic phase patients had 1 Ph<sup>1</sup> chromosome. Six of the 7 patients had cell cycle times ranging from 48-59 hr. Two hr after pulse labeling with <sup>3</sup>H-TdR, a transitional phase patient showed labeled metamyelocytes; patients in blastic phase required 6-20 hr for labeled metamyelocytes to appear and patients in stable phase required 22-24 hr. The mitotic index (per 1000 cells) ranged from 3-7.5 in the 7 patients. Both labeled and unlabeled neutrophilic precursors were capable of phagocytosis.

0228 ULTRASTRUCTURE OF ADENOID CYSTIC CARCINOMA OF SALIVARY GLAND ORIGIN.

(E.) Tandler, B. (Sch. Dent., Case Western Reserve U., Cleveland, Ohio). *Lab Invest* 24(6):504-512, 1971.

Stained sections of 5 adenoid cystic carcinomas were examined under the electron microscope; material included 2 cases of primary tumor in the parotid gland, 1 case of primary tumor in the sub-mandibular gland, 1 case of recurrent tumor of minor salivary gland origin and 1 case of recurrent tumor of parotid gland origin. In a light microscopic examination, all 5 tumors showed histological similarities; cells were arranged in cords and clusters with large intercellular spaces. Cystic spaces were seen surrounded by tumor cells and lined by a hyaline-appearing substance. Under the electron microscope, this substance consisted of basement membrane material having a complex layered structure. Foci of concentrically arranged microfibrils were seen in the interstices of these layers. Small stellate granules were seen on the periphery of the filamentous areas in the basement membrane. True lumina were occasionally found in the cellular areas of the tumors; some lumina contained crystalline material of unknown composition. Some cells with cytoplasmic filaments were seen but it could not be determined whether they were myoepithelial. Cells in one parotid gland tumor had extensive complexes of basal laminae and contained abundant organelles; cells in the other parotid gland tumor had poorly developed basal laminae and few organelles.

0229 THE MORPHOLOGICAL EFFECTS OF ESTROGEN REMOVAL ON AN ESTROGEN-DEPENDENT ADRENOCORTICAL CARCINOMA IN RATS. (E.) Nichols, R. M. (Dept. Path., U. British Columbia, Vancouver). *Cancer Res* 31(7):1042-1050, 1971.

An investigation by light and electron microscopy of the regression induced in a transplantable adrenocortical carcinoma by the removal of estrogen was

carried out. Twenty-five 2-month-old male hooded rats were given s.c. implants in the scapular region of an approximately 1 ml volume of tumor and then received s.c. estrone pellets. Four animals received a pellet but no tumor, and another was given a tumor implant but no pellet. Of those that received both tumor and pellet, 2, 8, and 3 were sacrificed when the tumor had reached 0.5, 1 and 2 cm respectively. Twelve had the pellet removed when the tumor had reached 1 cm; of these, 3 were sacrificed when the tumor had diminished to 0.5 cm and 3 were killed when it had reached a minimum size and remained stable for four weeks. The remaining animals had estrone pellets reimplanted when their tumors had remained at a minimum size for 4 weeks. A phase of secondary growth ensued, and 3 tumors each were examined when they had regrown to 1 and 2 cm. The prominent histological features of the regressing tumors were atrophy and infiltration by eosinophilic leukocytes. Eosinophils were seen in 2 situations: (a) the regressing tumors all contained vast number of eosinophils infiltrating between the trabeculae; (b) in the secondary growth tumors, the eosinophils were seen in significant numbers among the small cells which did not appear to be taking part in the renewed growth. Cells in the regressing tumors showed a reduction in the amount of ribosomes, an increase in cellular density and pigment granules, and a simplification of mitochondrial morphology.

0230 CHARACTERISTICS OF ESTABLISHED MYELOMA AND LYMPHOBLASTOID CELL LINES DERIVED FROM AN E MYELOMA PATIENT: A COMPARATIVE STUDY. (E.) Nilsson, K. (Wallenberg Lab., U. Uppsala, Sweden). *Int J Cancer* 7(3):380-396, 1971.

Myeloma and lymphoblastoid cells derived from the bone marrow of an E myeloma patient were established in culture and the growth requirements and characteristics of the 2 cell lines were compared; the lymphoblastoid line was designated 255 Bm and the myeloma line was designated 266 B1. 266 B1 cells grew only in media enriched with feeder cells such as adult skin fibroblasts or glia-like cells. Human sarcoma cells did not support the growth of 266 B1 cells. The population doubling time of myeloma cells in fed cultures depended on the type of feeder cells used, but it ranged from 5-7 days. 255 Bm cells grew in standard media without feeder cells. 255 Bm cells were thought to be of nonneoplastic origin. The population doubling time for these cells was 96-130 hr. 266 B1 cells showed no visible colony formation in agarose, while 255 Bm cells showed a colony-forming efficiency of 3-4% in agarose. Morphologically, 266 B1 cells were round to ovoid, while 255 Bm cells had a greater variety of shapes including pear-shaped cells with pseudopodia. 255 Bm cells were almost 50% larger than 266 B1 cells. The nucleo-cytoplasmic ratio was low in 266 B1 cells and high in 255 Bm cells; nuclei of 255 Bm cells were variable in shape and size, while nuclei of 266 B1 cells were uniformly ovoid. Golgi apparatus was clearly visible in the cytoplasm of 266 B1 cells, but absent from the cytoplasm of 255 Bm cells.



- 0231 THE ACTION OF HORMONES AND ACTINOMYCIN ON THE MITOTIC ACTIVITY OF TUMOR CELLS *IN VITRO*. (Rus.) Spitsa, A. I. (Dnepropetrovsk Med. Inst., U.S.S.R.) and V. I. Arkhipenko. *Voprosy Onkol* 17(4):80-84, 1971.

The combined effects of hormones and antibiotics on the mitotic activity of tumor cells *in vitro* was investigated. Experiments were performed with ovarian and pancreatic carcinoma (CaOv and CaPa) cell lines maintained in tissue culture. L-thyroxine (20 µg/ml) or insulin (0.2 U/ml) stimulated cell propagation by approximately 30%; these effects appeared to be manifest 8 hr after inoculation and reached maximal intensity in 16-24 hr. An increase in polynuclear giant cells and anomalous mitoses (predominantly anaphasic alteration) as well as the appearance of large amounts of chromosomes with no specific orientation could be observed 48 hr following hormone inoculation. Actinomycin (0.01 µg/ml), or aurantin (0.05 µg/ml), inhibited cell propagation 2 hr after inoculation. The stimulatory effects of thyroxine or insulin were inhibited in the presence of either actinomycin or aurantin.

- 0232 PROTEIN CONSTITUENTS OF SKIN TUMORS. (Ger.) Rodermund, O. E. (Bonn U., Germany.) *Arch Derm Forsch* 240(4):383-393, 1971.

Immunoelectrophoresis, cellulose acetate electrophoresis and fingerprinting were applied to study the protein composition of 12 human skin tumors. Malignant melanoma appeared to contain high albumin (70%) and low alpha- (12%), beta- (9%) and gamma-globulin (9%) levels. The wart specimens contained lower amounts of albumin (40-47%) and larger amounts of the globulin fractions (21-24% alpha-, 14-15% beta- and 14-25% gamma-globulin). Fibroblast cell sarcoma contained the lowest amount of albumin (17%) and the highest amount of beta-globulin (41%). Most of the investigated tumors appeared to contain lower amounts of plasma protein than the normal skin tissue. The applied methods are suggested to be used for an initial biochemical characterization of skin tumors.

- 0233 TRACE-METAL ANALYSIS OF CANCEROUS AND NON-CANCEROUS HUMAN TISSUES. (E.) Layman, I. L. (Materials Res. Lab., Pennsylvania State U., University Park), R. Roy, B. E. Knox, H. Suhr and W. E. Delaney. *J Nat Cancer Inst* (1):1-11, 1971.

Normal and neoplastic tissue samples were taken from individuals with cancer and emission spectrographic tests were performed to compare the trace metal contents of healthy and malignant tissue. Total ash, copper, magnesium, manganese and zinc were present in mammary tissue of patients with ductal

and/or scirrhous carcinoma of the breast in significantly greater amounts than in controls. The iron content of bronchial tissues from patients with bronchogenic carcinoma was lower than that in normal bronchial tissue. Zinc content of cancerous bronchial tissue, however, was higher than that in normal tissue. Other trace metals such as aluminum, barium, calcium, chromium, copper, magnesium, manganese and titanium, were found in equivalent concentration in normal and cancerous bronchial tissue. The tin content was lower in cancerous tissue from patients with adenocarcinoma of the colon than in non-cancerous tissue. Differences in trace metal contents appeared to be specific for particular types of cancer.

- 0234 NEUROHISTOLOGICAL INVESTIGATION OF A CAROTID BODY TUMOR. (Ger.) Temesreksi, D (Franz-Joseph Hosp. Vienna, Austria). *HNO* 19(6):181-187, 1971.

The neoplastically altered carotid body from a 17-yr-old female patient revealed hyperplasia in all types of cell and tissue. The decay of the original nerve fiber produced typical secondary degeneration phenomena consisting of the generation of new nerve fibers from neuroblasts existing within the tumor. These neuroblasts were found to be in close contact with the sensory cells and the regenerated nerve fibers appeared to be part of the somatic system. Two kinds of newly generated elements could be determined in the tumor tissue: efferent units, originating from the neuroblasts, and afferent elements, originating from the regenerative processes. The question whether the degeneration of the initial nerve cell led to the decay of the carotid glomus or vice versa could not be answered.

- 0235 ATYPICAL CRISTAE IN MITOCHONDRIA OF HUMAN GLIOBLASTOMA MULTIFORME CELLS. (E) Tani, E. (Kyoto U. Med. Sch., Kyoto, Japan), T. Ametani, N. Higashi and E. Fujihara. *J Ultrastruct Res* 36:211-221, 1971.

Atypical cristae were found on electron microscopic examination of glioblastoma multiforme cells taken from a 47-yr-old male. There were usually 1-8 atypical cristae in a mitochondrion, arranged linearly throughout the matrix. The abnormal cristae were of 2 types: a closed junction type in which apposed cristal unit membranes were ordered in a parallel manner, and a septate desmosome type in which the unit membranes were separated by an intracristal space about 70 Å in width. In the close junction type of atypical cristae, the individual cristal membranes were unusually electron dense. In the septate desmosome type, a series of oriented parallel lamellae or septae were seen crossing from one cristal membrane to the adjacent cristal membrane. These lamellae were usually composed of electron opaque bodies which appeared to adhere to the inner dense components of the apposed respective cristal membranes.

- 0236 ACTIVITY OF ALKALINE AND ACID NUCLEASES IN TUMORS OF THE HUMAN CENTRAL NERVOUS SYSTEM: HISTOCHEMICAL STUDY. (E.) Taper, H. S. (Dept. Neuropath., U. Louvain, Louvain, Belgium), J.-M. Brucher and L. Fort. *Cancer* 28(2):482-490, 1971.

Histochemical techniques were used to determine the presence or absence of acid and alkaline RNase and DNase activity in benign and malignant central nervous system tumors; malignant tumors sampled included medulloblastoma, glioblastoma, meningioma and reticulum cell sarcoma (31 tumors were assayed) and benign tumors included oligodendroglioma, astrocytoma, ependymoma and neurinoma (39 tumors were assayed). Malignant tumors very seldom revealed any activity of the nucleases; a very slight activity of only 1 nuclease could be seen in exceptional cases. In contrast, almost all benign tumors showed a positive reaction for all 4 nucleases; none of the tumors was negative for all 4 nucleases and most tumors were strongly positive for at least one nuclease. Necrotic areas of malignant tumors had a peripheral zone in which nuclease activity was detectable.

- 0237 BIOSYNTHESIS OF GLYCOSPHINGOLIPIDS BY MOUSE NEUROBLASTOMA (NB41A), RAT GLIA (RGC-6) AND HUMAN GLIA (CHB-4) IN CELL CULTURE. (E.) Dawson, G. (Joseph P. Kennedy, Jr. Mental Retardation Res. Ctr., Chicago, Ill.), S. F. Kemp, A. C. Stoolmiller and A. Dorfman. *Biochem Biophys Res Commun* 44(3):687-694, 1971.

Thin-layer chromatography was used to determine the relative amounts of various glycosphingolipids in cells from a mouse neuroblastoma line, and in cells from rat glial tissue and normal human skin fibroblasts. The neuroblastoma cell line synthesized at least 4 of the gangliosides characteristic of nervous tissue, including GM<sub>2</sub>, GM<sub>1</sub>, GD<sub>2</sub> and GD<sub>1</sub>. GM<sub>2</sub> was present in larger amounts in neuroblastoma cells than the other gangliosides. The glycosphingolipids asialo-GM<sub>2</sub> and asialo-GM<sub>1</sub> were also present in neuroblastoma cells. GM<sub>3</sub> (hematoside) was not found in neuroblastoma cells. On the other hand, hematoside was the predominant glycosphingolipid in rat glial cells and normal human skin fibroblasts. These cells types contained fewer varieties of glycosphingolipids than did neuroblastoma cells. GM<sub>3</sub> comprised 90% of the total glycosphingolipids in human fibroblasts and rat glial cells; other glycosphingolipids present in these cells were GL-1a, GL-2a and GD<sub>3</sub>. The absence of hematoside from neuroblastoma cells was thought to indicate that asialo-GM<sub>2</sub> acts as an intermediate in the synthesis and catabolism of gangliosides in neuroblastoma cells.

- 0238 HEXOKINASE ACTIVITY IN TUMORIGENIC AND NONTUMORIGENIC CELL CULTURES DERIVED FROM MOUSE ASCITES TUMOR CELLS. (E.) Bhatnagar, M. K. (Dept. Cancer Res., U. Saskatchewan, Saskatoon, Canada) and J. F. Morgan. *J Nat Cancer Inst* 47(1):15-20, 1971.

Hexokinase activity was assayed in ascites tumor cells taken from C3H/HeJ and strain A mice, and in tumorigenic and nontumorigenic cultures of mouse ascites tumor cells; 2 strains of ascites tumor cells were used, designated TA3 and 6C3HED. The nontumorigenic ascites tumor cells in culture had lost the capacity for inducing tumors in mice after prolonged periods in culture. Hexokinase activity was found to be lower in normal mouse liver and kidney than in mouse ascites tumor cells. TA3 and 6C3HED tumor cells taken directly from mice had similar or slightly higher levels of hexokinase activity than TA3 or 6C3HED tumor cells in tumorigenic cultures. The hexokinase activity level in nontumorigenic cell lines of both strains was lower than the hexokinase activity level in tumorigenic cell lines; non-tumorigenic TA3 cells showed a 28-30% reduction in enzyme compared to tumorigenic TA3 cell lines, and nontumorigenic 6C3HED cells showed a 21-28% reduction in enzyme activity compared to tumorigenic 6C3HED cells. In nontumorigenic cell lines of both strains, isozyme I was reduced compared to tumorigenic cell cultures or tumor cells taken directly from tumor-bearing mice.

- 0239 GUANYL CYCLASE ACTIVITY IN NORMAL ADRENALS AND A CORTICOSTERONE PRODUCING ADRENAL CANCER OF THE RAT. (E.) McMillan, B. H. (U. North Carolina Sch. Med., Chapel Hill), R. L. Ney and I. Schorr. *Endocrinology* 89(1):281-283, 1971.

Normal rat adrenals and tissue from an adrenocortical carcinoma were homogenized, and centrifuged at 1,000, 10,000 and 105,000 g to yield particulate fractions and a 105,000 g supernatant. Guanylate cyclase activity was measured in both fractions by the amount of cyclic guanosine-3',5'-monophosphate (cyclic GMP) formed in pmoles/mg protein/20 min. Most guanylate cyclase in normal adrenal was located in the 105,000 g supernatant (509 pmoles cyclic GMP/mg protein/20 min). In tumor tissue, there was relatively little guanylate cyclase in the 105,000 g supernatant (62 pmoles cyclic GMP/mg protein/20 min.); most guanylate cyclase activity in tumor tissue was located in the 1,000 g particles (209 pmoles cyclic GMP/mg protein/20 min). Guanylate cyclase activity was not stimulated in normal adrenal or tumor tissue by ACTH, angiotensin II, sodium fluoride, epinephrine or norepinephrine.

- 0240 HYPOGLYCAEMIA AND MALIGNANCY DIFFERENCES OF CLOSELY RELATED SUBLINES OF A RAT TUMOUR. (E.) Killington, R. A. (Dept. Microbiol., U. Birmingham, England), A. E. Williams, N. A. Ratcliffe, T. P. Whitehead and H. Smith. *Brit J Cancer* 25(1):93-105, 1971.

Male rats were given i.p. injections of 10<sup>7</sup> cells from 1 of 3 lines of the WBPl ascites tumor and the effects on serum glucose and SGOT were noted; the 3 tumor lines employed were WBPl(A) a malignant tumor line, WBPl(V), a more malignant subline than WBPl(A), and WBPl(X) derived from WBPl(V) by serial transplantation and thought to be more malignant than WBPl(V). A correlation was found between



the induction of fatal hypoglycemia during tumor growth in the rats and the malignancy of the tumor cell line used. Serum glucose and SGOT deviated from normal levels 8-10 days after injection of subline cells and 12-15 days after injection of subline cells. On day 15 postinoculation, the serum glucose level in rats given A subline tumor cells was 65 mg glucose/100 ml serum. WBPl(X) tumor cells produced a hypoglycemic reaction comparable to that produced by WBPl(V) cells.

- 0241 GLYCOGENOSIS TYPE I (GLUCOSE 6-PHOSPHATASE OF HEPATOCYTES IN A TUMOR BEARING LIVER. (E.) Boycher, M. A. (Dept. Path. Anat., U. Zürich, Switzerland) and R. Gitzelmann. *Virchows Arch Abt Zellpath* (2):133-142, 1971.

Liver cells and cells from a liver tumor arising in a 23-yr-old glucose 6-phosphatase-deficient woman were examined under the electron microscope. Biochemical analysis of liver and tumor tissue showed that glucose 6-phosphatase was absent in liver and in tumor nodules; an abnormally high glycogen content was found. Under the electron microscope, liver parenchyma cells showed marked alterations of the rough endoplasmic reticulum (ER); stacked ER lamellae were replaced by a continuous network of branched profiles which approached a vesicular structure. Smooth ER also had a vesicular aspect. Similar alterations were seen in the rough ER in cells from tumor nodules; in tumor cells, however, these alterations were often more pronounced than in liver cells.

- 0242 EXPRESSION OF DIFFERENTIATED FUNCTIONS IN HEPATOMA CELL HYBRIDS: I. TYROSINE AMINOTRANSFERASE IN HEPATOMA-FIBROBLAST HYBRIDS. (E.) Schneider, J. A. (Ctr. Molec. Genet., Gif-sur-Yvette, France) and M. C. Weiss. *Proc Nat Acad Sci USA* 68(1):127-131, 1971.

At hepatoma cells and mouse fibroblast cells were fused and the hybrid cells were assayed for tyrosine aminotransferase (TAT) activity. On karyotype analysis it was found that most of the hybrid cells had lost chromosomes. Hepatoma cells showed high TAT activity (18.2 mU/mg protein) and were inducible with dexamethasone phosphate (Dex) or actinomycin D. TAT activity in fibroblasts was nearly lacking (0.81 mU/mg protein) and could not be induced with Dex. Hepatoma-fibroblast cell hybrids were low in TAT (0.9-1.9 mU/mg protein), and were not inducible with Dex. Heating abolished all TAT activity in fibroblast cells but did not affect TAT in hepatoma cells; heated hybrid cells showed intermediate levels of TAT activity.

- 0243 SULPHYDRYL LEVELS OF SOME HUMAN TISSUES AND TUMOURS. (E.) Doxey, D. (Mount Vernon Hosp., and Radium Inst., Northwood, Middlesex, England). *Brit J Cancer* 25(1):46-52, 1971.

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Protein-bound and acid-soluble sulphhydryl levels (-SH) were determined from specimens of tissue taken from rectal carcinoma, colonic carcinoma, stomach carcinoma, breast carcinoma, gastric ulcer, spleens from patients with various neoplastic and nonneoplastic conditions, fetal liver, fetal lung, fetal brain and fetal muscle. In rectal carcinoma, protein-bound -SH increased with increasing acid-soluble -SH; when acid-soluble -SH levels were at 4.56, protein-bound -SH levels were at 4.98 and when acid-soluble -SH was at 5.09, protein-bound -SH was at 5.58. Again in rectal carcinoma, an acid-soluble -SH level of 5.64 corresponded to a protein-bound level of 6.45. In carcinoma of the colon, protein-bound, -SH levels decreased as acid-soluble -SH levels increased. No correlations between acid-soluble and protein-bound -SH levels were found in any of the other tissue studied. -SH levels in the stomach mucosa from gastric ulcer patients were lower than -SH levels of the mucosa of stomach carcinoma patients. In fetal tissue, -SH levels increased with age and reached a maximum in 4-month fetuses; -SH levels in more developed fetuses were lower.

- 0244 BIOCHEMICAL STUDY OF NUCLEI ISOLATED FROM NORMAL LUNG AND LUNG TUMORS: I. ISOLATION OF NUCLEI AND CHARACTERIZATION OF NUCLEAR RNA. (E.) Yazdi, E. (VA Hosp., Houston, Texas), F. Gyorkey, H. Busch and P. Gyorkey. *J Nat Cancer Inst* 47(1):121-127, 1971.

Nuclei were isolated from lung tissue cells taken from male subjects and from patients with squamous cell carcinoma, adenocarcinoma and anaplastic carcinoma, and the RNA/DNA ratios of the neoplastic and normal nuclei were compared. The average RNA/DNA ratio in nuclei of normal lung tissue cells was 1.65 and the average RNA/DNA ratio in nuclei of neoplastic lung tissue cells was 0.52. The nucleotide composition of nuclear RNA from normal and neoplastic lung tissue cells was also observed. The average uridylic acid composition of normal lung tissue cell nuclear RNA was 29.3 M% and that of neoplastic lung tissue cell nuclear RNA was 23.1 M%. The average cytidylic acid composition of normal lung tissue cell nuclear RNA was 18.3 M% and that for neoplastic lung tissue cell nuclear RNA was 23.5 M%. The base compositions of nuclear DNA from normal and neoplastic lung tissue cell were similar.

- 0245 CHROMOSOMES IN BRONCHIAL ADENOMAS AND IN BRONCHOGENIC CARCINOMAS. (E.) Falor, W. H. (Akron City Hosp., Akron, O.). *Amer Rev Resp Dis* 104:198-227, 1971.

Karyotype studies were carried out on biopsy specimens from patients with bronchial carcinoid adenoma, cylindromatous adenoma, epidermoid bronchogenic carcinoma, bronchogenic adenocarcinoma and undifferentiated bronchogenic carcinoma. Patients with adenomas showed modal chromosome

numbers in tumor tissue specimens of 45 and 46; in the cylindromatous adenoma, chromosome counts ranged from 40-93. All karyotypes of carcinomas were abnormal. Chromosome numbers from specimens of epidermoid carcinoma tissue ranged from 40-100; modal numbers in these specimens were most frequently 60-65 or 70. In adenocarcinomas and undifferentiated carcinomas, high quality metaphases were scarce and total chromosome counts lacked significance; however, the broad range of counts in this group was in the peridiploid region. Carcinoma karyotypes were abnormal structurally as well as numerically; all tumors showed an increase in chromosomes in groups E16 and F with decreases in groups B, D and G. Markers were present in all but 1 tumor karyotype.

- 0246 MELANOMAS OF THE GOLDEN HAMSTER: CHROMOSOMAL STUDIES. (Ger.) Witkowski, R. (Humboldt U. Berlin, Germany), R. Zabel and R. Heinze. *Derm Mschr* 157(6): 391-398, 1971.

Cytogenetic data from 3 strains of spontaneous transplantable hamster melanoma revealed minor deviations from the normal karyotype. The dark melanoma strain elicited 2 specific chromosomes, a long acrocentric marker chromosome (M-1), found to be present in 92% of the metaphases, and a marker chromosome (M-2) with a wide achromatic band within the centromere, found to be present in 50% of the karyograms. The light (amelanotic) and the mixed melanoma strains had karyograms similar to that of the dark strain melanoma with minor numerical variations towards the hypertriploid and the subtertraploid range. The M-2 chromosome was missing in the light strain melanoma and both M-1 and M-2 chromosomes were missing in the mixed melanoma strain; this strain elicited another marker chromosome, M-3. Acrocentric chromosomes are also characteristic of human tumor cells. However, the occurrence of marker chromosomes should not be considered as a criterion for tumor cell malignancy since they may be missing in metastasizing tumors.

- 0247 CHROMOSOME STUDIES IN A "CANCER FAMILY". (E.) Bottomley, R. H. (Oklahoma Med. Res. Fdn., Oklahoma City), A. L. Trainer and P. T. Condit. *Cancer* 28(2):519-528, 1971.

Karyotype studies were performed on 27 members of a rural American family comprising 405 members 37 of whom had been known to have cancer of some form. Cancer of the breast was the most frequent condition seen in the family (10 cases); other conditions included cervical cancer, leukemia, osteogenic sarcoma and fibrosarcoma. Chromosomal studies showed considerable aneuploidy even in branches of the family in which cancer was uncommon. Increased chromosomal abnormalities were seldom seen. Chromosome studies were performed on the mother of 2 children both of whom developed leukemia; the mother herself developed breast cancer and leukemia. Prior to the onset of leukemia, her chromosomal mode was

46 but after developing leukemia her chromosomal mode dropped to 45. The disposition to develop cancer in members of the family was thought to be inherited as an autosomal dominant trait.

- 0248 THE ASSOCIATION OF SQUAMOUS OESOPHAGEAL CANCER AND THYROID DISEASE. (E.) Arnott S. J. (Royal Infirmary, Edinburgh, Scotland), J. G. Pearson, N. D. C. Finlayson and D. J. C. Shearman. *Brit J Cancer* 25(1):33-36, 1971.

Interviews were conducted with 178 patients with squamous carcinoma of the esophagus to determine the incidence of thyroid disease in patients with this condition; there were 82 females and 96 males in the carcinoma patient sample. The incidence of thyrotoxicosis in the esophageal cancer patients was 1% among males and 8% among females, yielding an overall incidence of 5% for thyrotoxicosis in the esophageal cancer population. The age of the patients at diagnosis of esophageal cancer ranged from 66-84-yr-old, and the age at diagnosis of thyroid disease ranged from 29-78-yr-old. The incidence of thyrotoxicosis in this group of esophageal cancer patients was exceeded only by the incidence of previous gastric surgery for peptic ulceration among the patients.

- 0249 GENETIC VARIANTS OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE IN THE STUDY OF CARCINOMA OF THE CERVIX. (E.) Smith, J. W. (UCLA Sch. Med., Los Angeles, California), D. E. Townsend and R. S. Sparkes. *Cancer* 28(2):529-532, 1971.

Biopsy specimens from 5 patients with cervical dysplasia, 1 patient with carcinoma *in situ* and 7 patients with invasive cervical carcinoma were homogenized, centrifuged, and electrophoresed on cellulose acetate strips; electrophoretic variants of the X-linked enzyme glucose-6-phosphate dehydrogenase were observed in order to determine whether the neoplastic conditions being studied had a single cell origin or a multicellular origin. Single glucose-6-phosphate dehydrogenase bands were found in all biopsies from patients with cervical dysplasia and carcinoma *in situ*, indicating that these conditions have a single cell origin. In biopsies from patients with invasive disease, a single band was seen in 4 cases and double bands in 3. It was thought that a multicellular origin was likely for invasive carcinoma in 2 of the 3 patients showing double bands. In 1 patient who was undergoing radiation therapy for invasive carcinoma as the enzyme study progressed, an increasing portion of the areas involved by malignancy showed 2 glucose-6-phosphate dehydrogenase bands.

- 0250 GENETIC FACTOR IN MALIGNANT MELANOMA. (E.) Wallace, D. C. (Queensland Inst. Med. Res. Brisbane, Australia), L. A. Exton and G. R. C. McLeod. *Cancer* 27(5):1262-1266, 1971.



family histories of 113 malignant melanoma patients in the Brisbane, Australia area, were obtained in order to determine the incidence of malignant melanomas among first-degree relatives of affected persons. Of 923 first-degree relatives of melanoma patients, 11 were found to have melanoma. Sixty-eight first-degree relatives were found in families in which 2 or more cases of melanoma had occurred and among these 68 there were 3 cases of melanoma. It was calculated on the basis of these findings that the heritability of liability to malignant melanoma among Brisbane citizens was  $11.3\% \pm 0.8\%$ . The increased risk of a given relative developing melanoma when there is more than 1 person in the family with melanoma was thought to suggest that the inheritance of malignant melanoma is polygenic in nature.

1 DIFFUSION OF CANCER CELLS IN THE CHICK EMBRYO. III. ELECTRON MICROSCOPY OF THE CHORIOALLANTOIC MEMBRANE. (Fr.) Mouton, Y. (Inst. Cancer Res., Lille, France), A. Demaille and J. Lessens. *C R Soc Biol (Paris)* 164(12):2528-2532, 1971.

By means of electron microscopy, the chorioallantoic membrane of the chick embryo was observed following the injection of Ehrlich cells. The invasion by tumor cells through the capillary barrier involves the following events: a marked alteration in the chorioallantoic membrane at the point of contact with Ehrlich cells before penetration into the vessels; localized tumor cell formation, fragmentation, crumbling and accumulation before dissolution; a transparietal passage of the tumor cells with partial fusion of their cytoplasm with the nearest endothelial cytoplasm; an endothelialization of the tumor cells by penetration into the endothelial cells of the capillary itself (although the cytoplasmic membranes of the tumor cells appeared normal); and endothelial embolization of the tumor cells without associated thrombosis. These changes suggest a biochemical lytic action on the proteins present in these membranes.

2 COMPARATIVE EFFECTS OF HEATING AND FASTING IN MICE, WITH PARTICULAR REFERENCE TO DEVELOPMENT OF SARCOMA 180. (E.) Cioli, V. (Res. Center, A.C.R. Angelini F., Rome Italy) and B. Vestrini. *Brit J Cancer* 25(1):149-157, 1971.

Male C31 mice were subjected to varying temperatures beginning 7 days after the s.c. interscapular implantation of fragments of solid sarcoma 180; for a period of 4 wk, mice were maintained at temperatures of 22, 26, 28, 32, 35, 36, and 37°C. The mice were subjected to fasting; these were fed food every second day for 14 days. 6-Mercaptopurine was administered to mice daily for 7 days at a site remote from the tumor implant in amounts 10 mg/kg. Heating produced a significant inhibition of body wt of tumor-bearing mice; the weight of mice not exposed to heat was 32 g in tumor-bearing mice exposed to heat.)

Heating affected body wt to a lesser extent in normal mice than in tumor-bearing mice. In sarcoma-bearing mice the index of tumor mass at 4 wk after the beginning of the experiment was 7.73, while the index of tumor mass in heat-treated tumor-bearing mice at 4 wk was 4.36. Body wt was more markedly decreased by fasting than was tumor mass. Combined heating and fasting reduced both body wt and tumor mass index in tumor-bearing mice; body wt was more markedly reduced in mice subjected to heating and fasting than in mice exposed to either treatment alone. 6-Mercaptopurine reduced body wt and tumor mass index to a degree similar to that seen in mice given heating alone.

0253 LIVER METASTASES---AN EXPERIMENTAL STUDY. (E.) Garvie, W. H. H. (Dept. Surg., U. Aberdeen, Scotland) and R. M. Grant *Brit J Cancer* 25(1):166-171, 1971.

Female rats were given injections of Walker 256 tumor cells in sites remote from the liver and the effect of the growing tumor on liver glycogen synthesis was observed. In one experiment, tumor cells were injected s.c. into a hind leg; rats were fasted for 24 hr and given an i.p. injection of glucose. When livers were excised, a marked decrease in liver glycogen content was seen in the livers of rats bearing 8-20-day-old tumors as compared to livers of rats not given injections of tumor cells. In a second experiment, rats with 15 day-old hind leg tumors were starved for 24 hr and given an i.p. injection of glucose followed 2 hr later by an i.p. injection of glucagon (0.1 mg/100 g body wt). Immediately prior to glucagon treatment, the mean blood sugar for control rats not bearing tumors was 87 mg and that for tumor-bearing rats was 107 mg%; 10 min after glucagon, blood sugar of controls was 115 mg% and blood sugar of tumor-bearing rats was 114 mg%; by 20 min after glucagon, the blood sugar of controls and tumor bearing rats were 104 and 107 mg%, resp. In a third experiment, untreated rats were starved for 24 hr and given an i.p. injection of glucose; Walker tumor cells were administered to the abdomen. Of 35 starved rats, 17 had extensive liver tumors while only 2 of 36 rats not placed on a starvation regimen had extensive liver tumors. It is concluded that liver depleted of glycogen is more susceptible to the development of metastases from circulating cancer cells than normal liver.

0254 LYMPHOGRAPHY PRODUCES NO METASTASES OF TUMORS. (Ger.) Georgi, M. (Heidelberg U., Germany), H. Scheurlen, H. Munzinger, H. Poser and K. Goerttler. *Naturwissenschaften* 58(7):370. 1971.

The danger of tumor spread by carrying off neoplastic cells through lymphography with oily contrast media, used in exploratory search for metastases, was investigated. Sprague-Dawley rats were inoculated unilaterally (limb) with 0.2 ml (26,000-37,000 tumor cells/ml) of an ascitic Walker carcinoma following

lymph vessel puncture. Lymphography was then carried out on the same side 2 or 4 days later using Lipiodol (0.28 ml, injection time 10 min) and the rats were killed 11 days after tumor implantation. No differences between the incidence in lung metastases in control and lymphography-subjected rats were found under the experimental conditions.

0255 IMMUNOCYTOLOGICAL DEMONSTRATION OF LYSOZYME (MURAMIDASE) IN HUMAN LEUKAEMIC CELLS. (E.) Asamer, H. (Dept. Med., U. Innsbruck, Innsbruck, Austria) F. Schmalzl and H. Braunsteiner. *Brit J Haemat* 20(6):571-574, 1971.

0256 CHARACTERIZATION OF THE RAPIDLY LABELED HYBRIDIZABLE RNA SYNTHESIZED IN L5178Y MOUSE LEUKEMIC CELLS. (E.) Meltz, M. (Sch. Med. Dent., U. Rochester, Rochester, N.Y.) and S. Okada. *Biophys J* 11(7):582-595, 1971.

0257 HISTOCHEMICAL AND ULTRASTRUCTURAL STUDY OF KAPOSII'S ANGIOSARCOMA. (E.) Orbaneja, J. G. (Med. Fac., U. Madrid, Madrid, Spain), A. V. Jimenez, E. S. Yus and L. Diaz-Flores. *Rev Clin Esp* 121(1):13-20, 1971.

0258 CANCER OF THE GASTRIC STUMP AFTER GASTRECTOMY FOR ULCER. (Fr.) Haehnel, P. (Gen. Surg. Service., C.H.U., Strasbourg, France), J. Seror, D. Jaeck, G. Sava, J. Dauchel and J. F. Grenier. *J. Radiol Electr* 52(6-7):383-386, 1971.

0259 CHORIOCARCINOMA IN A MAN: COMPARISON OF MALIGNANT AND PLACENTAL TROPHOBLAST BY ENZYME HISTOCHEMICAL TECHNIQUES. (E.) Greenwood, S. M. (State U. New York, Downstate Med. Ctr., Brooklyn, N.Y.), A. F. Gelb and J. R. Goodman. *J Path* 103(3):201-204, 1971.

0260 ULTRASTRUCTURE OF AN OSTEOID TYPE OF OSTEOGENIC SARCOMA. (E.) Kay, S. (Med. Coll. Virginia, Richmond). *Cancer* 28(2):437-445, 1971.

0261 CANCER AND ALLERGY. (E.) Shapiro, S. (Lemuel Shattuck Hosp., Boston, Mass.), O. P. Heinonen and V. Siskind. *Cancer* 28(2):396-400, 1971.

0262 STUDIES OF THE MELANOCYTES OF THE EPIDERMIS ADJACENT TO TUMORS. (E.) Cochran, A. J. (U. and Western Infirm., Glasgow, Scotland). *J Invest Derm* 57(1):38-43, 1971.

0263 TERATOCARCINOGENESIS AS RELATED TO THE AGE OF EMBRYOS GRAFTED UNDER THE KIDNEY CAPSULE. (E.) Damjanov, I. (Inst. Biol., U. Zagreb, Zagreb, Yugoslavia). D. Solter and N. Skreb. *Wilhelm Roux' Arch* 167(1):288-290, 1971.

0264 AN INVESTIGATION OF THE MINOR BASE COMPOSITION OF TRANSFER RNA IN NORMAL HUMAN BRAIN AND MALIGNANT BRAIN TUMORS. (E.) Randerath, K. (Massachusetts General Hosp., Boston), S. K. Mackinnon and E. Randerath. *FEBS Letters* 15(1):81-89, 1971.

0265 INHIBITION OF GUANINE METABOLISM OF MAMMALIAN TUMOR CELLS BY THE CARBOCYCLIC ANALOGUE OF ADENOSINE. (E.) Hill, D. L. (Southern Res. Inst., Birmingham, Ala.), S. Straight, P. W. Allan and L. L. Bennett, Jr. *Molec Pharmacol* 1(4):375-380, 1971.

0266 "GEOGRAPHY" OF MITOSES AND CELL DIVISION IN THE BASAL CELL LAYER OF MOUSE EPIDERMIS. (E.) Karatschai, M. (German Cancer Res. Ctr. Heidelberg), V. Kinzel, Kl. Goerttler and R. Suss. *Z Krebsforsch* 76(1):59-64, 1971.

0267 CYTOPLASMIC LIPID IN EHRlich ASCITES TUMOR CELLS BEFORE AND DURING RECURRENT GROWTH. (E.) Burns, E. R. (U. Arkansas Med. Ctr. Little Rock) and B. L. Soloff. *Oncology* 25(3):283-288, 1971.

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0269 THE THYMOMA-PRONE (NZB x CFW) F1 MOUSE. (E.) Francis, D. (Inst. Child Hlth., U. London, London, England), R. D. Barnes and J. Kramer. *J Path* 103 (3):188-193, 1971.

0270 EVIDENCE FOR PROFLAVINE SENSITIVE PROTEINS IN MALIGNANT HAMSTER MELANOMA. (E.) Birkmayer, G. D. (Inst. Psych. Chem., U. Munich, Munich, Germany) and B.-R. Balda. *Hoppe Seyler Z Physiol Chem* 352(6):780-790, 1971.

0271 HISTOPATHOLOGICAL STUDIES ON LEUKEMIC LIVER AND SPLEEN, WITH SPECIAL REFERENCE TO THE SIZES OF LEUKEMIA CELLS INFILTRATING THE LIVER. (E.) Ito, E. (Tattori U. Sch. Med., Japan). *Yonago Acta Med* 14(3):106-130, 1971.



- 0272 SPONTANEOUS CANCERS IN *Pracomys (Mastomys) natalensis*. (E.) Hollander, C. F. (Org. Hlth. Res., Rijswijk, Netherlands) and J. McGinnison. *J Nat Cancer Inst* 46(6):1343-1348, 1971.
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- 0274 ABERRANT NUCLEAR DIVISION CONFIGURATIONS OCCURRING IN THE BONE MARROW OF CANCER PATIENTS. (E.) Perencevich, E. N. (Doctors Hosp., Columbus, O.). *J Amer Osteopath Ass* 70(2):114-120, 1971.
- 0275 FLUORESCENT PATTERN OF APPARENTLY NORMAL CHROMOSOMES IN BURKITT LYMPHOMAS. (E.) Manolov, G. (Inst. Genet., U. Lund, Lund, Sweden), Manolova, A. Levan and G. Klein. *Hereditas* 68(2):160-163, 1971.
- 0276 SOFT TISSUE SPREAD OF GIANT-CELL TUMOR: A CASE REPORT. (E.) Frangakis, E. K. (Hippokraton Hosp., Athens, Greece). *J Bone Joint Surg* 53A(5):994-998, 1971.
- 0277 PEPTIDE ELONGATION ENZYMES IN TUMOR CELLS AND MOUSE LIVER. (E.) Li, C.-C., (Harvard Med. Sch., Boston, Mass.) and C.-T. Yu. *Biochemistry* 10(16):3009-3013, 1971.
- 0278 ULTRASTRUCTURE OF SHEEP PULMONARY ADENOMATOSIS (JAAGSIEKTE). (E.) Nisbet, D. I. (Predun Res. Inst., Edinburgh, Scotland), J. M. K. McKay, W. Smith and E. W. Gray. *J Path* 103(3):157-162, 1971.
- 0279 MORPHOLOGIC CHANGES IN THE LIVER OF MICE BEARING EHRlich ASCITES TUMOR. (E.) S. H. (Dept. Path., McGill U., Montreal, Quebec, Canada) and H. Aleyassine. *Lab Invest* 26(6):513-522, 1971.
- 0280 DEFICIENCY OF UNCOUPLER-STIMULATED ADENOSINE TRIPHOSPHATASE ACTIVITY IN TIGHTLY PACKED HEPATOMA MITOCHONDRIA. (E.) Pedersen, P. L. (Johns Hopkins U. Sch. Med., Baltimore, Md.), T. A. H. P. Morris and W. A. Catterall. *Proc Nat Acad Sci USA* 68(5):1079-1082, 1971.
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**Editor**

Robert Love, M.D.  
Jefferson Medical College, Philadelphia

**Associate Editor**

George P. Studzinski, M.D.  
Jefferson Medical College, Philadelphia

**NCI Staff Consultants**

Elizabeth Weisburger, Ph.D.  
Sidney Siegel, Ph.D.

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BY

JOHN BURNET

OF

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IN TWO VOLUMES



## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain two-hundred abstracts and twenty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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## NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For those not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Journals*, 3rd Edition, are used.

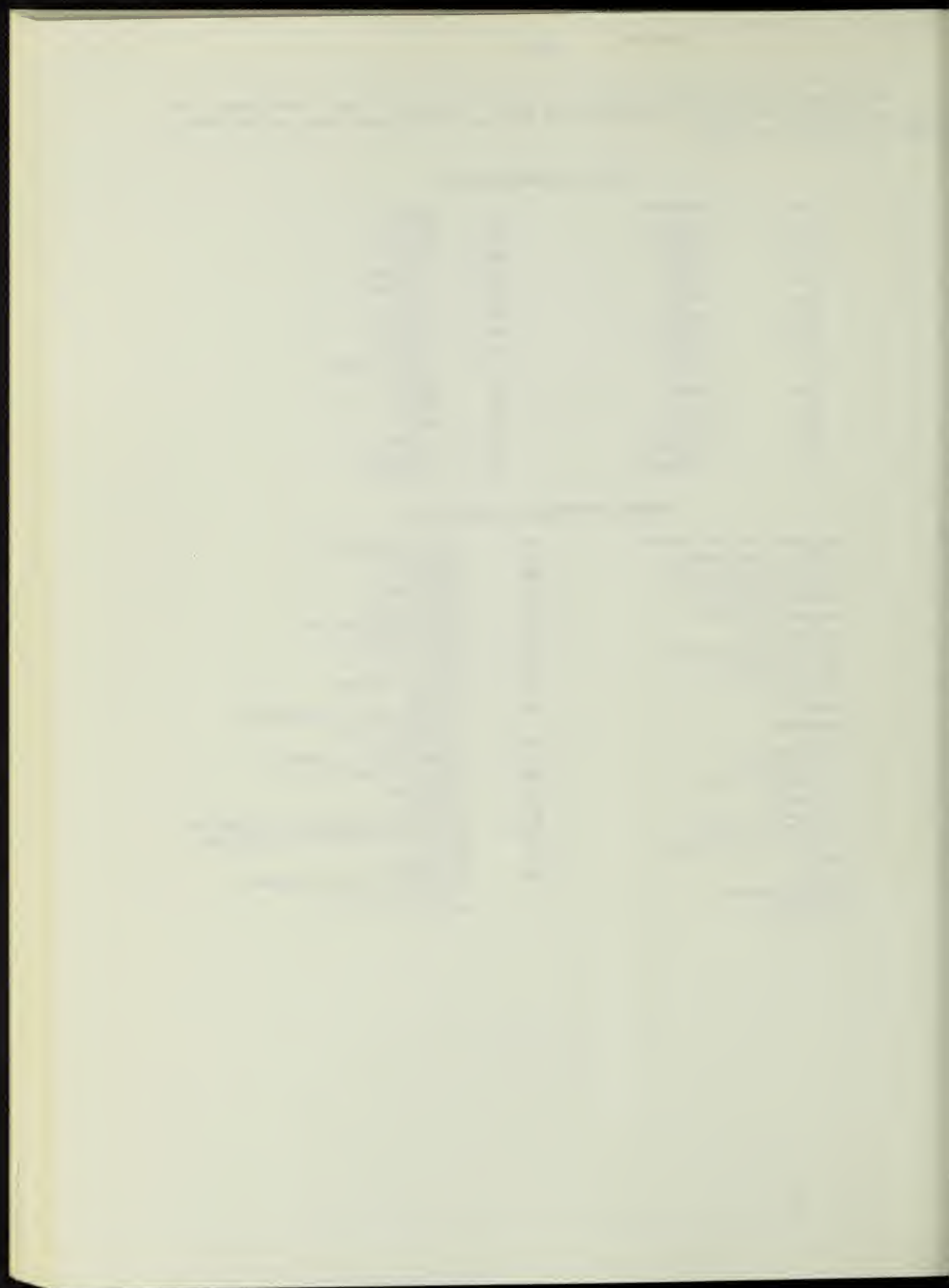
### LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ik.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

### ABBREVIATIONS USED IN ABSTRACTS

adrenocorticotrophic hormone	mC, $\mu$ C	milli-, microcurie(s)
adenosine diphosphate	mg	milligram(s)
adenosine monophosphate	min	minute(s)
adenosine triphosphate	ml	milliliter(s)
sulfobromophthalein	mm	millimeter(s)
degrees centigrade	MTD	maximum tolerated dose
centimeter(s)	ng	nanogram ( $10^{-9}$ )
central nervous system	pg	picogram ( $10^{-12}$ )
counts per minute	p.o.	orally
deoxyribonucleic acid	ppm	parts per million
for example	r	Roentgen
gram(s)	RBC	red blood cells (erythrocytes), red blood count
microgram(s)	resp.	respectively
hour(s)	Rev.	review (only in citations)
intramuscular	RNA	ribonucleic acid
intraperitoneal	s.c.	subcutaneous
international unit(s)	sec	second(s)
intravenous	SGOT	serum glutamic-oxalacetic transaminase
kilogram(s)	SGPT	serum glutamic-pyruvic transaminase
median lethal dose(s)	U	unit(s)
lactic acid dehydrogenase	UV	ultraviolet
meter(s)	WBC	white blood cells (leukocytes), white blood count
molar	yr	year(s)
milliequivalent(s)		
millimolar		
micromolar		





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1 THE KINETICS OF TUMOUR CELL PROLIFERATION AND RADIOTHERAPY. (E.) Tubiana, M. (Gustave Roussy Inst., Villejuif, France). *Brit J Radiol* 44(521):325-347, 1971.

radiosensitivity of a cell varies throughout cell cycle and the effect of a single radiation exposure on a cell population depends on the proportion of anoxic cells, the distribution of proliferating cells in the various phases of the cell cycle and on the proportion and properties of the quiescent non-cycling cells. The differences in cell cycle durations between normal and malignant tissues is relatively small. Similarly in solid tumors, there is little correlation between tumor volume doubling time and the cell cycle time. This indicates that differences in growth rate cannot be attributed to variations in cell cycle duration. Two factors which might explain differences in growth rate are the differences in the proportions of proliferating cells (growth fraction) and rates of cell loss. In solid tumors, these parameters may vary from the center of the tumor to its periphery and appear to be influenced by environmental factors. At least 4 types of factors influence the growth rate of a tumor: immune reactions against tumor cells; metabolic conditions such as oxygen concentration; reduction of the availability of metabolites and pH; cell crowding which acts through lack of space; medium effects or contact inhibition and specific inhibitors or lack of stimulation. Various types of quiescent non-cycling cells may exhibit differences in radiosensitivity and repair capacity after sublethal damage. Irradiation and cytotoxic drugs produce a disturbance of the kinetics of tumor cell proliferation. An acceleration of the growth rate of surviving tumor cells has been observed both in man and in the experimental animal. This may be due either to depopulation which itself increases the availability of nutrients or to the liberation of growth stimulating substances by necrotic cells. This repopulating ability of some tumors may be a reason for local failure to inhibit growth. (153 references)

THEORETICAL SIGNIFICANCE OF ARSENIC AS A CARCINOGEN. (E.) Rosen, P. (Dept. Physics, Amherst, U. Massachusetts, Amherst). *J Theor Biol* 25-426, 1971.

Results of a statistical study of the prevalence of arsenical skin cancer in Taiwan reported that the higher the content of arsenic in drinking water, the greater the frequency of patients with skin cancer. A theory of carcinogenesis is proposed in which a functional operon which is interconnected with the mitotic operons is blocked. It is suggested that the substitution of arsenic for phosphorus in the DNA molecule could illuminate the exact nature of the blockage of the operon. (4 references)

0303 TOXICITY OF NITROSAMINES: THEIR POSSIBLE HUMAN HEALTH HAZARDS. (E.) Magee, P. N. (Middlesex Hosp. Med. Sch., London, England). *Food Cosmet Toxicol* 9(2):207-218, 1971.

Recent findings concerning the carcinogenicity of N-nitroso compounds (nitrosamines and nitrosamides) are reviewed. Several nitrosamines have been shown to induce carcinoma in the liver, tongue and esophagus of rats; lung tumors have also been induced with nitrosamines. Animal species susceptible to the induction of liver carcinoma by diethylnitrosamine include rat, mouse, hamster, guinea pig, dog, pig, rabbit and monkey. Experiments with cells in culture have suggested that man is as sensitive as the rat to the carcinogenic action of dimethylnitrosamine. It has been shown that the hormonal changes associated with hypophysectomy and orchidectomy do not affect the incidence of brain and peripheral nerve tumors induced in rats by dimethylnitrosamine. Some evidence has been found, however, that sex influences tumor induction by nitrosamines. The ability of nitroso compounds to induce tumors of the nervous system in the offspring of animals treated with these agents during pregnancy has been firmly established; the transplacental effects of nitrosamides are more severe than those of nitrosamines, perhaps because nitrosamides are more unstable under physiological conditions than nitrosamines. Nitrosamides are also more effective than nitrosamines as teratogens and mutagens. It has been shown that polycyclic hydrocarbons and inorganic particulate matter such as ferric oxide particles enter into a synergistic relationship with nitrosamines for the induction of tumors. Studies of the presence of nitrosamines in the human environment have suggested that nitrosamines may be present in tobacco smoke, smoked food products, especially fish, and in certain distilled spirits in Africa. Formation of nitrosamines from secondary amines and nitrites under the conditions existing in the human stomach has been demonstrated and simultaneous feeding to rats of secondary amines and sodium nitrite has resulted in the production of tumors. (73 references)

0304 COLON CARCINOGENS: THEIR METABOLISM AND MODE OF ACTION. (E.) Weisburger, J. H. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.). *Cancer* 28(1):60-70, 1971.

Carcinogens of the human colon and cecum include 3-methyl-4-aminobiphenyl derivatives, azoxymethane, derivatives of 1,2-dimethylhydrazine (including cycasin), and a constituent of the bracken fern. Colon cancer is rare in animals; in man it is probably caused by ingestion of carcinogenic agents occurring in food products. Bacterial enzymes such as  $\beta$ -glucuronidase play an important role in the metabolic breakdown of colon carcinogens; the enzymes may release carcinogens or co-

carcinogens to the lower gut region following action on certain carcinogen precursors in food. In addition, procarcinogens, ingested in food, may be absorbed and metabolized by the liver and secreted in the bile, releasing active carcinogens in the gut region. (74 references)

- 0305 A POSSIBLE ROLE OF URINARY METABOLITES OF TRYPTOPHAN IN THE HETEROTOPIC RECURRENCE OF BLADDER CANCER IN MAN. (E.) Yoshida, O. (U. Wisconsin Med. Sch., Madison), R. R. Brown and G. T. Bryan. *Amer J Clin Nutr* 24:848-851, 1971.

Clinical evidence for a causal relationship between the abnormal production and excretion of tryptophan metabolites and bladder carcinoma is reviewed. Studies have shown that as many as 10 out of 10 patients with bladder carcinoma excreted abnormally large amounts of tryptophan metabolites (including anthranilic acid, kynurenine and 3-hydroxykynurenine). Although other studies have discovered bladder carcinoma patients who did not excrete increased amounts of tryptophan metabolites, it is clear that bladder carcinoma patients often show abnormally high levels of excretory tryptophan metabolites. In one study it was found that bladder carcinoma patients from a rural area in Wisconsin showed increased levels of excretory tryptophan metabolites more frequently than did bladder carcinoma patients from the Boston area. A correlation has also been found between increased excretion of tryptophan metabolites and "heterotopic recurrence" of bladder carcinoma (i.e., the occurrence of new tumors at a site different from the site of the original regressed or resected tumors). Among 38 bladder carcinoma patients, 20 had normal and 18 had abnormal tryptophan metabolism; all 18 patients in the latter group had 1 or more heterotopic recurrences of bladder tumors within 5 years after resection of the original tumors. It is suggested that long term administration of vitamin B<sub>6</sub> might retard the development of heterotopic recurrences of human bladder tumors. (16 references)

- 0306 EFFECTS OF ENVIRONMENTAL CHEMICALS ON THE METABOLISM OF DRUGS, CARCINOGENS, AND NORMAL BODY CONSTITUENTS IN MAN. (E.) Conney, A. H. (Wellcome Res. Labs., Tuckahoe, N.Y.), R. Welch, R. Kuntzman, R. Chang, M. Jacobson, A. D. Munro-Faure, A. W. Peck, A. Bye, A. Poland, P. J. Popper, M. Finster and J. A. Wolff. *Ann NY Acad Sci* 179:155-172, 1971.

Recent findings concerning the effects of environmental chemicals on microsomal enzyme activity in man are reviewed. Exposure to DDT, a potent stimulator of drug and steroid metabolism in animals, was

found to decrease the serum half-life of phenylbutazone and to increase the urinary excretion of 6 $\beta$ -hydroxycortisol in persons employed in the manufacture of DDT. The findings suggest that intense and prolonged exposure to DDT stimulates hepatic drug and steroid metabolism in humans. Piperonyl butoxide, a potentiator of insecticidal activity in compounds including naphthalene and carbamates, has been found to slow the metabolism of the carcinogen benzo(a)pyrene *in vivo* in animals. Although it was suspected that piperonyl butoxide might, by its effects on anti-pyrene metabolism, potentiate the carcinogenicity of compounds in the human environment, administration to humans did not affect antiprene metabolism. In studies on the possible effects of cigarette smoking on microsomal enzyme activity in man, benzo(a)pyrene hydroxylase was found in placentas of 100% of women who smoked 10-40 cigarettes/day and only in a few placentas of nonsmokers. In experiments with animals it has been established that hydroxylated metabolites of benzo(a)pyrene are more cytotoxic than benzo(a)pyrene itself. Steroid metabolism in human placenta has not been shown to be affected by cigarette smoking. (98 references)

- 0307 IMMUNOLOGICAL STUDIES WITH HUMAN NEOPLASMS. (E.) Morton, D. A. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.). *J Reticuloendothel Soc* 10(1):137-160, 1971.

Recent findings concerning the antibody-forming immune response of patients with melanoma and sarcoma to antigens associated with these tumors are reviewed. Immunofluorescence tests revealed that patients with a high resistance to melanoma showed a higher incidence of melanoma antibody (75%) than patients with advanced melanoma (50%). Sera from donors without melanoma showed antibodies to melanoma tissue in 18% of cases. Studies with mice have indicated that chemical carcinogen-induced, as well as virus-induced neoplasms produce common antigens in addition to individually tumor-distinct antigens. Several studies with melanoma patients have suggested that there is a common antigen to human malignant melanoma and that the presence of antibody to this antigen is inversely correlated with the degree of advancement of the state of the disease. Immunization of melanoma patients with bacillus Calmette-Guerin induced an enhanced immune response to melanoma antigens. A correlation of antibody response to stage of disease was found in sarcoma and melanoma patients. Antibodies to a liposarcoma antigen were found in 100% of sera from patients with liposarcoma, chondrosarcoma and fibrosarcoma, in 80% of sera from patients with osteosarcoma, and in 20% of sera from normal blood donors. Antisarcoma antibody titers were high in patients whose tumors had been excised and who had remained tumor-free after surgery; in contrast, antibody titers were low in a group of patients who had developed metastatic sarcomas following treatment. The antigen eliciting the antibody response in sarcoma patients appeared to be specific



to sarcoma. Enhanced antibody responses could be produced in sarcoma patients by immunizing them with bacillus Calmette-Guerin or with irradiated autologous tumor cells. (34 references)

0308 IMMUNOLOGICAL TOLERANCE TO RNA TUMOR VIRUS GENOME EXPRESSIONS: SIGNIFICANCE OF TOLERANCE AND PRENATAL EXPRESSIONS IN EMBRYOGENESIS AND TUMORIGENESIS. (E.) Huebner, R. J. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), P. S. Sarma, G. J. Kelloff, R. V. Gilden, H. Meier, D. D. Myers and R. L. Peters. *Ann NY Acad Sci* 181:246-271, 1971.

Recent findings concerning the natural occurrence of expressions of the RNA tumor virus genome are reviewed; 3 classes of genome expression are discussed: the infectious virion and its type-specific envelope antigen, the group-specific (gs) antigen, and the capacity to induce tumors. RNA tumor virus virions are uncommon in most free-living animal species; however, RNA tumor virus gs antigens have been detected in a wide variety of species. C-type RNA tumor viruses have been found to induce leukosis and renal carcinoma in chickens, leukemia and sarcoma in mice, and leukemia in cats. Host gene controls of certain RNA tumor viruses have been well documented; the infectious leukemia and sarcoma viruses of chickens and mice have host ranges limited by the differing genetic makeup of specific strains. Infectious avian leukosis virus has been shown to be transmitted vertically as well as horizontally through chicken populations. Lymphomas in virus-infected mice are also transmitted vertically. The RNA tumor gs antigen may also be transmitted vertically in chickens. Studies have suggested that the expression of the complement-fixing antigen in livers of chick embryos was determined by a Mendelian dominant gene. (110 references)

0309 CIVILIZATIONAL CONDITIONS OF PROLIFERATIVE DISEASES. (E.) Aleksandrowicz, J. (Acad. Med., Cracow, Poland). *Ann NY Acad Sci* 184:167-176, 1971. (12 references)

0310 EXPERIMENTAL MODELS IN ENVIRONMENTAL CARCINOGENESIS. (E.) Kuschner, M. (New York U. Sch. Med., N.Y.) and S. Laskin. *Amer J Path* 64(1):183-191, 1971. (13 references)

0311 BASIC TRENDS IN THE RESEARCH OF CANCER CHEMOTHERAPY, OF MECHANISMS OF CHEMICAL CARCINOGENESIS, OF BIOLOGY AND BIOCHEMISTRY OF THE TUMOR CELL IN THE U.S.A. (FROM MATERIAL FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH). (Rus.) Belousova, A. K. (Inst. Exp. Clin. Oncol., U.S.S.R.) *Vop Onkol* 17(4):102-111, 1971. (96 references)

0312 PART IV. IMMUNOLOGICAL TOLERANCE TO AND SUPPRESSION BY ONCOGENIC VIRUSES: TOLERANCE TO DNA TUMOR VIRUSES. (E.) Defendi, V. (Wistar Inst., Philadelphia, Pa.). *Ann NY Acad Sci* 181:236-245, 1971. (24 references)

0313 PARASITOSIS AND CANCER. (Fr.) Yumner, B. (No affiliation) *Med Afrique Noire* 18(4):321-329, 1971. (47 references)

0314 HORMONES AND CANCER. (Fr.) Dargent, M. (No affiliation) *Med Afrique Noire* 18(4):307-319, 1971. (No references)

0315 THE HERPESVIRUS. (Fr.) Bornand, J. E. (Swiss Fdn., Paris, France). *Rev Med* 91(5):309-318, 1971. (16 references)

0316 HUMAN CANCER AND VIRUS. (Fr.) Baylet, R. (Inst. Med. Phar., Dakar, Senegal), S. Dauchy and S. Diop. *Med Afrique Noire* 18(4):333-348, 1971. (No references)

0317 IDENTIFICATION OF ANTECEDENTS TO COLORECTAL CANCER. (E.) Burdette, W. J. (U. Texas M. D. Anderson Hosp., Houston). *Cancer* 28(1):51-59, 1971. (54 references)

0318 THE ORIGIN OF VIRAL TUMORS. (Ger.) Falke, D. (Inst. Med. Microbiol., Mainz, Germany). *Deutsch Med Wschr* 96(27):1167-1172, 1971. (39 references)

0319 INVASIVE TUMOR GROWTH: COMPARATIVE HISTOLOGICAL, ELECTRON MICROSCOPICAL AND BIOCHEMICAL STUDIES OF EAK-TUMOR IMPLANTS IN MICE. (Ger.) Rath, F. W. (Martin-Luther U., Halle, Germany), U. Bonk, C. Coutelle, R. Coutelle, D. Felicetti and F. Traub. *Deutsch Gesundh* 26(20):905-910, 1971. (127 references)

0320 CLINICAL OBSERVATIONS AND LITERATURE REVIEW ON ASBESTOS EXPOSURE HAZARDS; 1) PULMONARY ASBESTOSIS. 2) DIFFUSE MALIGNANT PLEURAL MESOTHELIOMA. 3) ASBESTOS AND LUNG CANCER. (Sp.) Del Amo, L. L. (Vizcaya Hlth. Group., Spain). *Med Segur Trab* 19(73):21-40, 1971. (120 references)



- 0321 BIOLOGICAL FEATURES OF MALIGNANT BONE TUMORS. (It.) Prodi, G. (Inst. Exp. Oncol, U. Bologna, Italy), A. Di Marco and G. Franceschi. *Chir Organi Mov* 59(4):321-330, 1971. (18 references)
- 0322 CHRONIC ANTIGENIC STIMULATION AS A PATHOGENIC FACTOR IN THE DEVELOPMENT OF MALIGNANT LYMPHOMAS. (Dan.) Myking, A. O. (No affiliation). *Nord Med* 85(21):645-676, 1971. (48 references)
- 0323 CANCER IN BLACK AFRICA: SOCIAL AND ECONOMIC FEATURES, DETECTION, PROPHYLAXIS, EDUCATION. (Fr.) Gaye, P. (No affiliation) and A. Dia. *Med Afrique Noire* 18(3):191-199, 1971. (15 references)
- 0324 SPONTANEOUS GASTRIC ADENOCARCINOMAS OF DOGS: A REVIEW. (E.) Lingeman, C. H. (Publ Hlth. Ser., Natl. Inst. Hlth., Bethesda, Md.), F. M. Garner and D. O. Taylor. *J Nat Cancer Inst* 47(1):137-149, 1971. (124 references)
- 0325 IMMUNOLOGICAL TOLERANCE AND SUSCEPTIBILITY OF NEWBORN MICE TO INOCULATION OF LEUKEMIA. (E.) Gross, L. (VA Hosp., Bronx, New York). *Ann NY Acad Sci* 181:279-280, 1971. (5 references)
- 0326 TUMOUR-SPECIFIC ANTIGENS: THEIR POSSIBLE SIGNIFICANCE IN THE ETIOLOGY AND TREATMENT OF MALIGNANT DISEASE. (E.) Moore, M. (Robert Jones and Agnes Hunt Orthop. Hosp., Oswestry, England). *J Bone Joint Surg* 53(1):13-22, 1971. (66 references)
- 0327 VIRUS AND CANCER: APPROACHING A SOLUTION OF THE ENIGMA? (Sp.) Suarez, H. G. (Cancer Res. Inst., Villejuif, France). *Medicina* 31(2):134-142, 1971. (28 references)
- 0328 ORIGIN AND SPREAD OF CANCER. (It.) Sirtori, C. (No affiliation) *Gaz Sanit* 42(1-2):48-50, 1971. (38 references)
- 0329 MULTIPLE TUMORS OF THE UPPER RESPIRATORY AND DIGESTIVE TRACT. (It.) Manara, G. (Pavia U., Italy), L. Vaggi. *Boll Mal Orecch* 87(6):489-536, 1969. (77 references)
- 0330 ONCOGENIC VIRUSES. (Fr.) Bayon, N. (No affiliation) *Gaz Med France* 78(24):3991, 3993-3994, 1971. (No references)
- 0331 THE ROLE OF CLIMATIC FACTORS IN THE DEVELOPMENT OF SKIN EPITHELIOMA IN SAILORS AND FISHERMEN. (It.) Jakac, D. (Rijeka Med. Sch., Yugoslavia). *Chron Derm* 2(1):43-57, 1971. (9 references)
- 0332 SYMPTOMS OF RADIATION DISEASE AND LATER SEQUELAE IN MAN WITH SPECIAL REFERENCE TO THE VICTIMS OF THE ATOMIC EXPLOSIONS IN HIROSHIMA AND NAGASAKI. (Pol.) Szirmai, E. (Inst. Nucl. Hematol., Cracow, Poland), G. Medgyesi and Z. Srebro. *Przegl Lek* 28(3):253-257, 1971. (29 references)
- 0333 CONNECTIONS BETWEEN THE TECHNOLOGY OF TOBACCO PRODUCTS AND THE INCIDENCE OF PULMONARY CANCER. (Pol.) Rokicki, W. (Acad. Med., Cracow, Poland). *Przegl Lek* 28(4):311-313, 1971. (16 references)
- 0334 OBSERVATIONS ON THE VICTIMS OF THE ATOMIC EXPLOSIONS AT HIROSHIMA AND NAGASAKI. (Pol.) Szirmai, E. (Inst. Nucl. Hematol., Cracow, Poland) and G. Medgyesi. *Przegl Lek* 28(4):305-308, 1971. (12 references)

0335 THE RELEVANCE OF CHEMICO-BIOLOGICAL INTER-ACTIONS FOR THE TOXIC AND CARCINOGENIC EFFECTS OF AROMATIC AMINES: IV. METABOLIC PATTERNS OF TRANS-4-DIMETHYLAMINOSTILBENE, CIS-4-DIMETHYLAMINO-STILBENE AND 4-DIMETHYLAMINOBIBENZYL IN LIVER, KIDNEY AND EXCRETION PRODUCTS OF THE RAT. (Ger.) Metzler, M. (Max-Planck Inst. Biochem., Munich, Germany) and H.-G. Neumann. *Z Krebsforsch* 76(1):16-39, 1971.

Metabolism of trans-4-dimethylaminostilbene (trans-DAS), cis-DAS and 4-dimethylaminobibenzyl (DABB) in Wistar rats given a single dose (1.2 mg p.o.) of carcinogen was investigated. No qualitative differences in the metabolic pathways of the 3 compounds could be discovered. The dimethylamines appeared to be demethylated and the primary amines were then acetylated. Hydroxylation appeared to occur after the acetylation of the unsubstituted amines and hydroxylation products such as 4'-hydroxy-, N-hydroxy-, 3-hydroxy-acetylaminos and 3-hydroxy-amines could be identified. The 3-hydroxy-amines and 4'-hydroxy-acetylaminos were excreted as sulfates, while the N-hydroxy- and 3-hydroxyacetylaminos were excreted as glucuronides in urine. The major part (80-90%) of the fecal metabolites were not conjugated. N-Hydroxylation of methylamines and amines occurred also. Considerable qualitative differences between both the amounts of produced metabolites and the excretion patterns were found. Binding of trans-DAS metabolites in the liver (25 µMol/g liver) 5 hr following administration of the compound was comparable to other well known carcinogens. The 4'-hydroxy-acetylamine derivatives of each compound appeared as sulfates in the liver. Demethylation of trans-DAS seemed to occur more intensively as compared to the other 2 compounds. Excretion of trans-DAS metabolites appeared to occur mainly through feces while excretion of the bibenzyl derivative metabolites occurred mainly through urine. Sufficient information could not be obtained to explain the different carcinogenicity of these compounds.

0336 EXPERIMENTAL INDUCTION OF TUMORS OF THE LARGE BOWEL OF RATS: A REVIEW OF THE EXPERIENCE WITH 3-2'-DIMETHYL-4-AMINOBIPHENYL. (E.) Spjut, H. J. (Baylor Coll. Med., Houston, Texas) and M. W. Noall. *Cancer* 28(1):29-37, 1971.

Male and female rats were given repeated injections of 3,2'-dimethyl-4-aminobiphenyl (DMAB) in doses of 2 mg/100 g body wt for periods of up to 3 mo.; injected rats ranged in age from newborn to adult. In some cases, rats had been oophorectomized and in other cases, the distal segment of the colon had been surgically bypassed to remove it from contact with the fecal stream. The total administered dose of DMAB ranged from 0.12-903 mg. Multiple polypoid lesions were seen in the colon of rats of all dosage groups except for a group which received DMAB injections for 1 wk only. Carcinomas of the large intestine were also seen. Six of 23 rats given DMAB for 3 mo. and 5 of 10 oophorectomized rats developed polypoid lesions. These lesions were protuberant and often had a short stalk; they resembled colonic polypoid lesions

in humans. Transition from a benign polypoid lesion to a malignant tumor was not observed. In rats in which the distal segment of the colon had been removed from contact with fecal matter there was no neoplastic development in the bypassed region.

0337 NATURE OF OESTROGEN SPECIFIC BINDING SITES IN THE NUCLEI OF MOUSE UTERI. (E.) Harris, G. S. (Cancer Res. Genet. Lab., U. California, Berkeley). *Nature* 231(25):246-248, 1971.

Uteri from 3wk-old BALB/c mice were incubated with <sup>3</sup>H-estradiol under conditions in which most of the bound estradiol was localized in the nuclei. When such nuclear preparations were treated with DNAase in the absence of added Mg<sup>2+</sup>, between 60 and 80% of the bound hormone was solubilized. When Mg<sup>2+</sup> was used together with DNAase, the release of the hormone was found to be considerably inhibited. Ca<sup>2+</sup> and Mn<sup>2+</sup> exerted a similar effect. The isolated receptor sedimented around 5S on sucrose density gradients containing 0.4 M KCl similar to the KCl extract of the nuclei. A nuclear estradiol complex sedimenting in the 8S region could be obtained from nuclei if the receptor which solubilized either with DNAase or KCl extraction was treated with a polyanion such as "Polytak-RNA", dextran sulfate or heparin. It is not clear whether the action of polyanions on the receptor in yielding an 8S receptor complex was the result of the removal of any specific protein of metabolic importance that had been associated with the receptor in the nucleus.

0338 CARCINOGENICITY OF 5-OXO-5H-BENZO[e]ISOCHROMENO[4,3-b]INDOLE AND ITS DERIVATIVES AND ANALOGUES: STRUCTURE-ACTIVITY RELATIONSHIPS. (Fr.) Lacassagne, A. (Radium Inst., Paris, France), N. P. Buu-Hoi, F. Zajdela, C. Stora, M. Mangane and P. Jacquignon. *C R Acad Sci (Paris)* 272(24):3102-3104, 1971.

The carcinogenic effects of a new group of derivatives of isochromeno(4,3-b)indole were studied in Swiss mice in comparison to those of 5-oxo-5 H-benzo(e) isochromeno(4,3-b)indole(II). The latter, a pentacyclic lactone, had previously been described as highly sarcomagenic. According to these studies (s.c. administration of 0.6 mg of compound in 0.2 ml of olive oil 3 times at monthly intervals), the carcinogenic effect varies considerably with the molecular structure. Thus, for example, the introduction of a single methyl group into this molecule is instrumental in the complete disappearance of the carcinogenic effect. In order to be active these compounds must be pentacyclic and must contain an isochromene group. Compound II, in spite of its polycyclic lactone structure, was found to be noncarcinogenic to mouse liver when administered orally to Swiss mice. This compound is selectively fixed in the connective tissues, where it is carcinogenic.



- 0339 THE EFFECT OF ACTINOMYCIN D ON CELL TRANSFORMATION INDUCED BY THE MOLONEY MURINE SARCOMA VIRUS. (Fr.) Godard, Ch. (Res. Inst. Leukemia Dis. Blood, Paris, France), B. Guillemain and M. Boiron. *C R Acad Sci (Paris)* 272(17):2269-2272, 1971.

Monolayer cell cultures (BALB/c mouse) were infected with Moloney murine sarcoma virus and the effect of actinomycin D upon the morphological conversion of these cells was investigated to determine whether this transformation was associated with early events of the viral cycle preceding those of replication. Cellular conversion was studied at various stages following infection with either  $0.2 \times 10^{-3}$  focus forming units (FFU) or 0.5-1.0 FFU. Cellular transformation was blocked by 6 hr treatment with 0.25  $\mu\text{g}/\text{ml}$  of actinomycin D in both low and high dose virus-infected cell cultures; this indicated that both cell transformation and viral replication are equally susceptible to the antibiotic. Apparently, the events of the viral cycle which are involved in the cell conversion process do not precede those implicated in viral replication. The events which appeared to be most susceptible to 0.25  $\mu\text{g}$  actinomycin occurred within 2 hr and 30 min following infection. Cellular conversion and viral propagation were inhibited when subjected to 72 hr of treatment with 0.025  $\mu\text{g}/\text{ml}$  of actinomycin. However, both processes continued their usual path when exposed to the same dose (0.025  $\mu\text{g}/\text{ml}$ ) of actinomycin for 6 hr before or after viral infection.

- 0340 SUSCEPTIBILITY OF MICE OF DIFFERENT STRAINS TO THE MAMMARY CARCINOGENIC ACTION OF NATURAL AND SYNTHETIC OESTROGENS. (E.) Rudali, G. (Radium Inst., Paris, France), E. Coezy, F. Frederic and F. Apiou. *Rev Europ Etud Clin Biol* 16:425-429, 1971.

Castrated and intact mice of various strains were treated with dietary estrogen (0.1 mg/kg or 1 mg/kg of mestranol) or given s.c. implanted estrogen pellets (5-10 mg estradiol) and the ensuing incidence of mammary tumors was observed. Castrated (C3H x RIII)  $F_1$  males aged 10 and 70 days developed tumors in 94 and 100%, resp., of cases 176 or 187 days after implantation with an estradiol pellet. Castrated RIII males developed tumors in 82% of cases 127 days after estradiol implantation; the tumor incidence among C3H mice implanted with pellets was 72% and the latency, 201 days. NLC mice were more resistant to estradiol carcinogenesis, developing tumors in 16% of cases 171 days after pellet implantation; and C57BL mice were totally resistant, none of 19 mice given implanted pellets developed tumors. Castrated male (C3H x RIII) $F_1$  mice grafted with an ovary in the ear developed more mammary tumors after a shorter latency than did female mice given ovarian grafts. Among female RIII mice given dietary mestranol the tumor incidence was 65% and among intact males given mestranol the tumor incidence was 42%; castrated males

given mestranol developed tumors in 85% of cases. Female (C3H x RIII) $F_1$  mice given mestranol developed tumors in 90% of cases, while castrated males given mestranol developed tumors in 92% of cases.

- 0341 CYTOPLASMIC CHANGES DURING THIOACETAMIDE INDUCED HEPATOCARCINOGENESIS IN RATS. (E.) Shetty, T. K. (Bhabha Atomic Res. Ctr., Bombay, India), L. M. Narurkar and M. V. Narurkar. *Brit J Cancer* 25(1):109-120, 1971.

Cytoplasmic changes were investigated in rat liver at different intervals of time up to 50 wk during primary induction of hepatoma by thioacetamide, a weak hepatocarcinogen. Thioacetamide was fed to Wistar strain rats in a dose of 0.032% in a 16% protein diet. Under these conditions it takes around a year of continuous feeding to induce malignant hepatomas. Microsomal glucose-6-phosphatase and ATPase activities progressively decreased with increased period of thioacetamide feeding, the fall in activities being more pronounced during the first 15 weeks. Hormonal induction of tryptophan pyrrolase and tyrosine transaminase activities was shown to undergo significant decreases of 65% and 55% resp. at the end of 50 wk feeding. Substrate induced tryptophan pyrrolase activity (L-tryptophan in a dose of 1 g/kg body wt was injected i.p. to rats 4 hr before killing) was decreased to 50% during the 50 wk period whereas substrate induced tyrosine transaminase activity (L-tyrosine in a dose of 0.6 g/kg body wt was injected i.p. to rats 4 hr before killing) gradually increased to 200%. The latter is attributable to differences in the optimal induction dose of tyrosine in normal and carcinogen fed rats. The m-RNA template lifetime for tryptophan pyrrolase was shown to exceed 24 hr in normal rats as against 13 hr in rats fed with the carcinogen 30 wk. The m-RNA template lifetime for tyrosine transaminase however was 3 hr for control rats and 7 hr for carcinogen fed rats. The observed changes were shown to occur long before the onset of malignant transformation. The alterations in terms of decreased glucose-6-phosphatase and substrate induced tryptophan pyrrolase activities were shown to be reversible when the carcinogen was withdrawn from the diet after 30 wk of feeding. After 40 wk however the changes became irreversible. It is postulated that sustained damage to the protein synthesizing intracellular membranes may be a prerequisite to an irreversible alteration in cellular metabolism which may lead to malignant transformation.

- 0342 EVIDENCE OF ETHYLATION OF RAT LIVER DEOXY-RIBONUCLEIC ACID AFTER ADMINISTRATION OF ETHIONINE. (E.) Swann, P. F. (Middlesex Hosp. Med. Sch., London, England), A. E. Pegg, A. Hawks, E. Farber and P. N. Magee. *Biochem J* 123(2):175-181, 1971.

Male rats were given a single large i.p. dose of  $^3\text{H}$ -labeled L-ethionine (500 mg/kg body wt) and killed after 18 hr; nucleic acids isolated from the livers



of these rats contained small amounts of the radioactive label. This DNA was chromatographed on Dowex 50 with the result that all the radioactivity in the liver cell DNA samples was eluted from the column in a region coincident with a sample of 7-ethylguanine. No radioactivity was found in the pyrimidine nucleotide fractions or in the fractions corresponding to guanine and adenine. DNA from livers of rats given injections of 800 mg/kg  $^3\text{H}$ -L-methionine was analyzed by chromatography on Dowex 50. There was considerable radioactivity in the fractions corresponding to pyrimidine nucleotides, guanine and adenine, but no radioactivity in 7-methylguanine. There was evidence that the radioactivity accumulated in liver cell DNA of L-ethionine-treated rats was not due to contamination of the isolated DNA by labeled protein, RNA, S-adenosyl-L-ethionine or L-ethionine. These findings indicated that as a result of a single dose of ethionine, there was a small but definite ethylation of DNA in rat liver cells. The finding that ethionine, a liver carcinogen, reacted with DNA in liver cells suggested that DNA may be the "target molecule" for ethionine carcinogenesis.

- 0343 ON THE METABOLIC ACTIVATION OF THE CARCINOGEN N-HYDROXY-N-2-ACETYLAMINOFLUORENE: III. OXIDATION WITH HORSERADISH PEROXIDASE TO YIELD 2-NITROSOFLUORENE AND N-ACETOXY-N-2-ACETYLAMINOFLUORENE. (E.) Bartsch, H. (German Cancer Res. Ctr., Heidelberg) and E. Hecker. *Biochim Biophys Acta* 237(3): 567-578, 1971.

Horseradish peroxidase and  $\text{H}_2\text{O}_2$  oxidize N-hydroxy-2-acetylaminofluorene (N-OH-AAF) to a free nitroxide radical which is detected by its ESR signal. Following the appearance of the free radical, 2-nitrosofluorene and N-acetoxy-N-2-acetylaminofluorene (N-OAc-AAF) were isolated as the major reaction products. More N-OAc-AAF was recovered from the reaction at pH 7 than at pH 5. Addition of tRNA to the reaction mixture of peroxidase,  $\text{H}_2\text{O}_2$  and  $^3\text{H}$ -labeled N-OH-AAF yielded labeled tRNA; no significant amount of labeling was incorporated into RNA in the absence of  $\text{H}_2\text{O}_2$ . Addition of guanosine to the basic reaction mixture yielded N-(guanosin-8-yl)-2-acetylaminofluorene. No N-OAc-AAF was found when N-OH-AAF reacted with the rat liver oxidase system.

- 0344 MUTAGENICITY TESTS WITH CYCLOHEXYLAMINE IN THE MOUSE. (E.) Cattanaach, B. M. (M.R.C. Radioactivity Unit, Didcot, Berks., England) and C. E. Pollard. *Mutat Res* 12:472-474, 1971.

Male  $\text{F}_1$  offspring of matings of C3H female mice with strain 101 male mice were given i.p. injections of cyclohexylamine totalling 250 or 500 mg/kg and mated with females; mated females were sacrificed at 14-16 days gestation and the proportion of pre- and post-implantation deaths caused by dominant lethal mutations induced by cyclohexylamine was ascertained. There was no indication that cyclohexylamine at the

doses given induced significantly elevated frequencies of pre- or post-implantation deaths. In a related experiment, testis preparations from cyclohexylamine-treated and from untreated male mice were examined for chromosome translocations; 1 of the 8 untreated controls showed a translocation while none of the 12 mice given either 50 or 100 mg/kg cyclohexylamine showed translocations. The results suggested that cyclohexylamine, even at high dose levels, does not induce heritable chromosome breakage either in the postmeiotic germ cells or in the spermatogonia of the mouse.

- 0345 TRANSPLACENTAL AND NEONATAL ETHYLNITROSO-BIURET-INDUCED CARCINOGENESIS IN BD IX RATS. (Ger.) Druckrey, H. (Max Planck Inst. Immun. Biol., Freiburg, Germany) and Ch. Landschütz. *Z Krebsforsch* 76(1):45-58, 1971.

Adult BD IX rats given 400, 800 or 1000 mg/kg of ethylnitrosobiuret (ENBU) in a single dose developed malignant tumors of the gastrointestinal tract after 450, 400 and 260 days, resp., following p.o. administration. The forestomach appeared to constitute the main target of ENBU carcinogenicity in adult rats. Transplacental carcinogenesis was investigated by p.o. administration of 100 or 200 mg/kg of ENBU (single dose) to pregnant rats on the 15th or 22nd day of gestation. The lower dose induced 50 malignant tumors in 28 of 29 offspring when administered on the 15th day of gestation and 56 malignant tumors of the nervous system in 42 of 45 offspring following ENBU administration on the 22nd day of gestation after an average latency period of 260 and 250 days, resp. The higher dose induced 32 malignant tumors in all of 14 offspring and 46 malignant tumors of the nervous system in the 34 offspring when administered on the 15th and 22nd day of gestation, resp., after an average latency period of 210 and 220 days, resp. All rats, treated at 10 days of age with 40 or 80 mg/kg ENBU (s.c. single dose), developed neurogenic tumors after an average latency period of 300 days in both cases. The importance of the time factor in ENBU carcinogenesis is emphasized and the time table of its application, chosen under the above experimental conditions, is recommended as a model.

- 0346 THE DIFFERENTIAL INTERACTION OF AFLATOXIN  $\text{B}_2$  WITH DEOXYRIBONUCLEIC ACIDS FROM DIFFERENT SOURCES AND WITH PURINES AND PURINE NUCLEOSIDES. (E.) Schabert, J. C. (Council Sci. Indust. Res., Pretoria, South Africa). *Chem Biol Interact* 3:371-382, 1971.

Aflatoxin  $\text{B}_2$  was mixed with DNA isolated from sources including calf thymus, salmon testis, *Salmonella typhimurium*, *Clostridium pasteurianum* and an obligated anaerobic bacterium; the interaction of aflatoxin  $\text{B}_2$  and DNA was examined using different analytic techniques. Differential spectroscopy of mixtures of DNA and aflatoxin  $\text{B}_2$  indicated a difference in the degree of interaction of aflatoxin

B<sub>2</sub> with different types of DNA which seemed to be dependent on base composition; the largest spectral shifts were produced by calf thymus DNA and salmon testis DNA. These DNAs had a G-C content of 41-43%. Equilibrium dialysis of aflatoxin B<sub>2</sub>-DNA mixtures showed a similar dependence of the interaction of aflatoxin B<sub>2</sub> with DNA on base composition. Again, equilibrium dialysis showed that the optimum G-C content of DNA for DNA-aflatoxin interaction was 41-43%. Difference spectroscopy showed that an increase in temperature of the aflatoxin B<sub>2</sub>-DNA mixture caused a decrease in interaction of aflatoxin and DNA. It was also found that aflatoxin B<sub>2</sub> binds to thermally denatured calf-thymus DNA. Precipitation of DNA by streptomycin and extraction of the toxin from aflatoxin B<sub>2</sub> by treatment with chloroform seemed to break the bond between DNA and aflatoxin B<sub>2</sub>. Further, difference spectroscopy indicated that aflatoxin B<sub>2</sub> could bind to calf-thymus histone and to highly polymerized yeast RNA. Purine bases and the presence of amino acid groups in purine molecules evidently played an important role in the binding of aflatoxin B<sub>2</sub> to DNA.

- 0347 CELL PROLIFERATION IN THE EARLY STAGES OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE-INDUCED HEPATOCARCINOGENESIS. (Ger.) Rabes, H. (München U., Germany), R. Hartenstein and W. Ringelmann. *Naturwissenschaften* 58(7):370-371, 1971.

Sprague-Dawley rats were fed 0.05% 3'-methyl-4-dimethylaminoazobenzene (MDAB) in the daily diet and autoradiographic investigations with labeled thymidine were carried out to study liver cell proliferation in the early stages of carcinogenesis. A 16% increase in label index within the bile duct epithelia was seen 14 days after the beginning of the experiment; this index decreased below 7% 7 days later and reached a minimal value on the 42nd day of treatment. The mesenchymal cells exhibited a proliferation peak on the 17th day followed by a decrease to below 50% of its maximal value on the 42nd day of treatment. Maximal liver cell proliferation was observed between 17-21 days after the beginning of the treatment. Apparently, an increase in DNA synthesis occurs in the early stages of MDAB treatment but a slow-down of cell proliferation seems to occur before tumor development becomes manifest.

- 0348 STUDIES ON THE MECHANISM OF ARL HYDROCARBON HYDROXYLASE INDUCTION AND ITS ROLE IN CYTOTOXICITY AND TUMORIGENICITY. (E.) Gelboin, H. V. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and F. J. Wiebel. *Ann NY Acad Sci* 179:529-547, 1971.

HeLa cells and cells from 2 mouse strains (NIH 3T12 and NIH 3T3) were treated with benz(a)anthracene and the effect of this agent on the aryl hydrocarbon hydroxylase enzyme system (AHH) of the cells was observed; it was found that benz(a)anthracene induced AHH in HeLa and mouse cells. AHH was also induced in virally- or chemically-transformed hamster cells by benzo(a)pyrene; however,

levels of AHH in benzo(a)pyrene-treated transformed cells were not as high as levels of AHH induced by this agent in untransformed hamster cells. Blocking protein synthesis in cell cultures with cycloheximide was found to prevent the induction of AHH by benz(a)-anthracene. AHH induction by benz(a)anthracene was dependent on RNA synthesis in test cells; actinomycin D, added to benz(a)anthracene-treated cultures, prevented AHH induction. However, when RNA synthesis was allowed to proceed for 2 hr after the introduction of benz(a)anthracene and before treatment with actinomycin D, actinomycin D did not inhibit AHH induction. It was found that cells in which a high level of AHH activity was found were especially sensitive to cytotoxic effects of benzo(a)pyrene, while cells with low levels of AHH were resistant to the cytotoxicity of this agent. Pretreatment of cells with 7,8-benzoflavone (BF) inhibited the metabolism of benzo(a)pyrene in cells by the AHH system; in addition, BF inhibited the cytotoxic effect of 7,12-dimethylbenz(a)anthracene (DMBA) on hamster cells. In studying the role of the AHH system in binding polycyclic hydrocarbons to nucleic acids it was found that the formation of DNA-hydrocarbon complexes depended on a microsome-catalyzed reaction. In studies of hydrocarbon tumorigenesis in mouse skin it was found that BF--which inhibited AHH--inhibited skin tumorigenesis induced by DMBA by up to 90%. Benz(a)anthracene which induced AHH--failed to affect skin tumorigenesis induced by DMBA; the results suggested that inhibition of tumor formation was related to the inhibition of AHH activity rather than to the induction of the AHH system.

- 0349 ARL HYDROCARBON HYDROXYLATION INDUCTION IN CELL CULTURE AS A FUNCTION OF GENE EXPRESSION. (E.) Nebert, D. W. (Natl. Inst. Child Hlth. and Human Development, Bethesda, Md.) and L. L. Bausserman. *Ann NY Acad Sci* 179:561-579, 1971.

The induction of aryl hydrocarbon hydroxylase activity by benz(a)anthracene (BA) in fetal and neonatal hamster cells, and in strain C57BL/6N and strain DBA/2N fetal mouse cells was examined. Apparently because of genetic differences between the 2 strains, the ability of BA to induce aryl hydrocarbon hydroxylase activity in C57BL/6N mouse cells is maximal while BA induction of the enzyme in DBA/2N mouse cells is minimal. In hamster experiments, fetal hamsters were injected with BA *in utero*; liver cell aryl hydrocarbon hydroxylase activity appeared 2-3 days before birth and increased 50-fold within 8 days postnatally in livers of hamsters not given BA. In livers of hamsters given BA, enzyme activity increased 90-fold 8 days after birth. In experiments with mice, C57BL/6N and DBA/2N mouse cells were treated with 13 µM or 1.3 µM BA and the induction of aryl hydrocarbon hydroxylase was observed. Rates of enzyme activity at either dose level of BA were 4-fold greater in C57BL/6N mice than in DBA/2N mice. The rate of entry of BA into cells of the 2 strains of mice, and the covalent binding of BA in mouse cells were studied. It was found that the intracellular level of hydrocarbon in DBA/2N cells usually exceeded that in C57BL/6N cells, indicating that the decrease in BA-inducible



aryl hydrocarbon hydroxylase in the former strain was not due to diminished cellular uptake of BA. There was no difference between the 2 mouse strains in the rate of covalent binding of BA in cells, ruling out deficient hydrocarbon binding as a cause of impaired aryl hydrocarbon hydroxylase inducibility in DBA/2N mice. It was found that the inability to stimulate hydroxylase activity in DBA/2N cells was not due to an increased rate of degradation of induced enzyme in these cells. Exposure of cells from the 2 mouse strains to BA for 24 hr produced more marked increases in total heme and in CO-binding cytochromes in C57BL/6N cells than in DBA/2N cells. This difference in the rate of newly formed hemoprotein synthesis was thought to account for the differential ability to stimulate hydroxylase in the 2 strains, for the hemoprotein was essential for aryl hydrocarbon hydroxylase activity. In addition, it was found that cells of DBA/2N mice showed a decreased expression of RNA specific for aryl hydrocarbon hydroxylase induction when compared to C57BL/2N cells.

0350 INFLUENCE OF DOSE ON SKIN TUMORS INDUCED IN MICE BY SINGLE APPLICATION OF 7,12-DIMETHYLBENZ(a)ANTHRACENE. (E.) Turusov, V. (Inst. Exp. and Clin. Oncol., Moscow, U.S.S.R.), N. Day, L. Adrianov and D. Jain. *J Nat Cancer Inst* 47(1):105-111, 1971.

Female (C57BL x CBA) F<sub>1</sub> mice were given topical applications of 7,12-dimethylbenz(a)anthracene (DMBA) in doses of 25, 50, 100, 200, 400, 800 or 1600 µg and the ensuing incidence of papillomas was observed. Doses of 25 and 50 µg DMBA produced focal desquamation and papilloma incidences of 35 and 42% resp.; doses of 100, 200 or 400 µg DMBA produced tumor incidences of 71, 75 and 81% resp. Doses of 800 or 1600 µg DMBA produced tumor incidences of 69 or 75%, resp. With doses of 200 µg or higher, the first papillomas appeared after 4-5 weeks whereas with doses of 100 µg or lower, papillomas did not appear until after 35-40 weeks. Of the 195 papillomas developing at the site of application of DMBA, 23 regressed, usually between 9 and 16 weeks after treatment. Malignant papillomas appeared in all mice given doses of DMBA exceeding 25 µg; papillomas became malignant more quickly in animals given higher doses of DMBA than in animals given lower doses. Among mice given 400-1600 µg DMBA a biphasic pattern of tumor development was seen; the first peak of high tumor incidence occurred within 4-8 weeks post-treatment and was then followed by a period of 9-24 weeks when only a few papillomas appeared. The second peak occurred between 25-96 weeks.

0351 SEX DIFFERENCE AND CARCINOGENIC DOSAGE IN THE INDUCTION OF NEOPLASMS IN SALIVARY GLANDS OF RATS. (E.) Glucksmann, A. (Strangeways Res. Lab., Cambridge, England) and C. P. Cherry. *Brit J Cancer* 25(1):212-224, 1971.

Two to 3-month-old male and female hooded rats were given injections of a 0.5% or a 1% solution or a 2% suspension of the carcinogen 7,12-dimethylbenz(a)an-

thracene (DMBA) dissolved in acetone. Animals in the control group were given a similar quantity of acetone. In one group of females a 30 mg pellet of pure testosterone propionate was implanted s.c. at the same time as the injection of 1% DMBA was administered. Stilbestrol was given to one group of males in their drinking water in a concentration of 0.1 mg/1000 ml thus dosing each rat with about 2 µg/day. Each of the groups of 21 to 44 rats was examined at weekly intervals. Carcinomas which developed were of two types- squamous cell tumors and mixed carcinomas (i.e. contain a secretory columnar as well as a keratinizing squamous cell strain). Sarcomas which developed were of several types. Of 529 sarcomas induced in 684 rats 60% were rhabdomyofibrosarcomas, 34% fibrosarcomas, 3% myxofibrosarcomas and 3% hemangiofibrosarcomas. The incidence of the different types of carcinomas and sarcomas did not vary significantly with the sex of the animals. However there were significant differences in the incidence of carcinomas and of sarcomas with sex and these were dependent on the dose of the carcinogen injected. At low concentrations of DMBA (0.5% and 1%) twice as many sarcomas and carcinomas of the salivary glands were induced in male as in female rats. Additional estrogens reduced neoplasms in males by one half while testosterone doubled them in females. The sex difference disappeared at the higher dose levels of the carcinogen (2%). The pattern of induction of carcinoma development differed from the incidence of sarcoma development in both male and female rats. In both sexes the threshold carcinogenic dose was lower for sarcomas than carcinomas; more sarcomas than carcinomas were induced by the same dose of DMBA up to a maximal level for both which was higher for sarcomas than for carcinomas. Carcinomas did not appear after 240 days while sarcomas appeared as late as 770 days. This difference in pattern of induction was postulated to be due to the formation of a fibrous capsule separating persisting DMBA- deposits from the epithelial structures and thus protecting them from carcinogenic risk.

0352 BIOASSAY FOR ANTIOXIDANTS BASED ON PROTECTION OF ISOLATED RAT LIVER MITOCHONDRIA AGAINST THE PHOTODYNAMIC TOXICITY OF BENZO(a)PYRENE. (E.) Epstein, S. S. (Harvard Med. Sch., Boston, Mass.), I. B. Saporoschetz, C. Katsioulas and Y. Bishop. *Food Cosmet Toxic* 9(3):367-377, 1971.

Rat liver mitochondria were exposed to benzo(a)pyrene and long-wave UV in the presence of antioxidants and the photodynamic toxicity of the carcinogen, as affected by the test antioxidants, was measured by the extent of mitochondrial swelling produced. Swelling was measured by reduction of the optical density of mitochondria. Ninety-two antioxidants were tested, including phenols, tocopherols, amines, polyenes and UV absorbers. Sixteen antioxidants were highly potent as protectors of mitochondria from the photodynamic toxicity of benzo(a)pyrene. Eleven of the 13 aminoazobenzenes tested gave good protection; none



of the UV absorbers was more than moderately potent. Findings in the mitochondrial bioassay for protective potency of antioxidants agreed with findings in an antioxidant bioassay which used protection from photodynamic injury to a protozoan as an index.

- 0353 THE EFFECT OF MOROXYDINE ON METHYLCHOLANTHRENE-INDUCED CARCINOGENESIS IN MICE. (Hun.) Glaz, E. (Simmelweis Med. Inst., Budapest, Hungary) *Magy Onkol* 15(2):86-89, 1971.

The role of latent viruses in hydrocarbon-induced oncogenesis in Swiss mice was investigated. Thirty-six mice were given a single dose of methylcholanthrene (MC) in olive oil solution (80 µg/mouse s.c.); moroxydine was administered via drinking water (200-300 mg daily) for 60 days to 26 mice and for 150 days to the other 10 mice. A control group of 35 mice received only MC. Fibrosarcoma developed in almost all the experimental animals after a latency period of 50 days. No relevant differences could be seen between the 3 experimental groups. The failure to increase the latency period in MC carcinogenesis by moroxydine treatment may indicate that the latent virus is not sensitive to this drug, that it may develop a certain resistance to the drug, that the inhibition of viral synthesis by this drug may be preceded by the malignant transformation of the cell, or that the viral genome was a constitutive part of the genetic apparatus of the cell at the time of the administration of the antiviral drug. However, the inefficiency of moroxydine under the experimental conditions appears to indicate that no latent viruses are involved in hydrocarbon-induced oncogenesis in mice.

- 0354 FREE RADICAL MEDIATED LINKAGE OF CARCINOGENIC HYDROCARBONS TO POLYNUCLEOTIDES. (E.) Pascal, Y. (Physico-chemical Biol. Inst., Paris, France), F. Pochon and A. M. Michelson. *Biochimie* 53(3):365-368, 1971.

The reaction of aromatic hydrocarbon free radicals (produced indirectly by irradiation in the presence of iodine) on DNA and synthetic polynucleotides was studied. Covalent bonding of hydrocarbons to DNA was observed with 3-methylcholanthrene, benzo(a)pyrene and dibenz(a,h)anthracene; these carcinogenic hydrocarbons bound 1-5 molecules/1000 nucleotides of DNA. No measurable covalent bonding to DNA was found for the noncarcinogenic hydrocarbons benz(a)anthracene, anthracene, chrysene and phenanthrene. The UV absorption spectra of DNA bound to carcinogenic hydrocarbons showed a band of absorption between 300-400 mµ; some cross-linking appeared to occur, although there was no denaturation of DNA.

- 0355 METHYLATION OF DNA IN THE INTACT ANIMAL AND THE EFFECT OF THE CARCINOGENS DIMETHYLNITROSAMINE AND ETHIONINE. (E.) Craddock, V. M. (Med. Res. Council, Carshalton, Surrey, England). *Biochim Biophys Acta* 240(3):376-383, 1971.

Female rats were given an i.p. injection of <sup>14</sup>C-methionine and DNA from liver cells of treated animals was analyzed by column chromatography. 5-Methylcytosine was found to be the only methylated base present. 5-Methylcytosine was also the only methylated base found in liver cell or testis cell DNA of rats given injections of radioactive methionine, formate or adenine following partial hepatectomy; no evidence for the formation of 3-methylcytosine was found in liver or testis DNA from these animals. DNA synthesis and DNA methylation were also investigated in precancerous liver cells of rats fed a diet containing 50 ppm dimethylnitrosamine for 23 wk prior to treatment with radioactive methionine or adenine. In precancerous livers, the methylation of DNA was found to be proportional to the synthesis of DNA. Rate of DNA synthesis and rate of DNA methylation had each doubled in carcinogen-treated rats by comparison to controls not given dimethylnitrosamine. In rats fed ethionine prior to treatment with radioactive methionine, column chromatographic analysis of liver cell DNA yielded 2 abnormal peaks which were apparently not due to contamination of DNA with RNA. Administration of radioactive ethionine to rats after partial hepatectomy did not result in the formation of 5-ethylcytosine; this suggested that DNA methylase does not utilize S-adenosylethionine to form 5-ethylcytosine.

- 0356 PROBABLE CLONAL GENESIS OF CELLULAR ISLANDS INDUCED IN RAT LIVER BY DIETHYLNITROSAMINE. (E.) Scherer, E. (Max-Planck Inst. Virus Res., Tübingen, Germany) and M. Hoffmann. *Europ J Cancer* 7:369-371, 1971.

Female rats were given single oral doses of diethylnitrosamine (DENA) (10 mg/kg) following 2/3 hepatectomy; <sup>3</sup>H-methyl-thymidine was injected i.p. into rats at the same time that they were given DENA treatment. Rats were killed 6 wk later and "islands" of glucose 6-phosphatase- and/or nucleoside-5'-polyphosphatase-deficient tissue in liver remnants were examined for distribution of the <sup>3</sup>H label. Labeling was significantly lower in "islands" than in surrounding normal tissue. This finding suggested that enzyme-deficient "islands" of liver tissue in DENA-treated rats were formed by cell division from single liver parenchymal cells transformed by DENA.

- 0357 COMBINED TRANSPLACENTAL AND POSTNATAL TREATMENT WITH N-NITROSODIETHYLAMINE (NDEA): CARCINOGENESIS IN MICE. (Rus.) Likhachev, A. Ya. (N. N. Petrov Res. Inst. Oncol., Leningrad, U.S.S.R.) *Vop Onkol* 17(4):64-69, 1971.

Induced carcinogenesis in mature mice through trans-

placental exposure to N-nitrosodiethylamine (NDEA) was investigated. Forty-five pregnant mongrel white mice were each given a single i.p. dose of 120 mg NDEA per kg of body weight 24-48 hr before delivery. Forty-four of the transplacentally-treated offspring and 56 controls (not subjected to transplacental treatment) were given a total of 300 mg NDEA/kg body weight. Treatment began 100 days after the initial dose and consisted of s.c. doses of 50 mg NDEA/kg body weight administered at 3-10 day-intervals. The first tumor which was observed occurred in a mouse subjected to transplacental treatment; death occurred at 232-days-of-age. Of 36 surviving transplacentally-treated mice and 44 controls, 36 and 37 mice resp. developed neoplasia. Differences in tumor incidence were observed by the 11th month and were maintained to the end of the experimental period. Pulmonary adenocarcinoma was found in 11 transplacentally-treated mice and 4 controls. The lung appeared to be the most frequent target for neoplasia in both experimental groups. Liver neoplasia (hepatocellular adenoma) was second in incidence for both groups. Multiple primary tumors were seen in 32 (86%) transplacentally-treated mice and 19 (43%) controls. It appears that transplacental administration of NDEA enhances the carcinogenic action of the compound given postnatally.

- 0358 KINETICS OF NITROSAMIDE FORMATION FROM ALKYLUREAS, N-ALKYLURETHANS, AND ALKYL-GUANIDINES: POSSIBLE IMPLICATIONS FOR THE ETIOLOGY OF HUMAN GASTRIC CANCER. (E.) Mirvish, S. S. (U. Nebraska Med. Ctr., Omaha). *J Nat Cancer Inst* 46 (6):1183-1193, 1971.

The nitrosation of alkylureas, N-alkylurethans and alkylguanidines was investigated. Methylurea was rapidly nitrosated; when 0.005 M methylurea and 0.01 M nitrite were reacted at pH 2, methylnitrosourea was produced in yields of 25% after 5 min of reaction and 95% after 1 hr. The initial reaction rate was proportional to methylurea and nitrite concentrations at pH 2 and increased 10-fold for each 1 U drop in pH. The main nitrosating species in the methylurea reaction was thought to be the nitrous acidium ion ( $\text{H}_2\text{NO}_2^+$ ). The nitrosation of ethylurea, N-methylurethan and N-ethylurethan proceeded more slowly than that of methylurea. For all 3 compounds, the rate of the reaction increased nearly 10-fold for each 1 U drop in pH. The rate of citrulline nitrosation was proportional to nitrous acid and citrulline concentrations between 0.005 and 0.02 M. The rate of the reaction increased 5-fold per pH U. Nitrosation of methylguanidine gave a 35% yield of methylnitrosourea, but the rate constant for the reaction at pH 2 was only 0.6% of the citrulline rate constant. The nitrosation of arginine and N- $\alpha$ -acetylarginine was examined; after reaction under highly acidic conditions, butanol extracts showed UV maxima at positions similar to those for nitrosocitrulline and ethylnitrosourea. The finding that alkylureas are readily nitrosated was thought to explain findings that nitrite and alkylurea, fed to rats, were associated with gastric formation of alkylnitrosoureas. Furthermore, intragastric nitrosamide formation may be

a factor in the genesis of human stomach cancer, since nitrites, nitrates, alkylureas and alkylguanidines occur commonly in human food products.

- 0359 TISSUE-DEPENDENT DIFFERENCES IN DNA METHYLATION PRODUCTS OF MICE TREATED WITH METHYL-LABELLED METHYLNITROSOUREA. (E.) Frei, J. V. (Fac. Med., U. Western Ontario, London, Canada). *Int J Cancer* 7(3):436-442, 1971.

Mice of the CFW/D strain were given injections of 50, 69 or 75 mg/kg  $^3\text{H}$ - or  $^{14}\text{C}$ -labeled methylnitrosourea; 30 min or 1 hr after treatment, mice were killed and bone marrow, spleen, thymus, kidney, liver and lung tissues were prepared for extraction of DNA. DNA from the various tissues was hydrolyzed and chromatographed to demonstrate the presence and proportions of 7-methylguanine, 3-methyladenine and 6-methoxyguanine. All 3 of the methylation products were detected in all tissues tested at all doses of methylnitrosourea used. 7-Methylguanine was the dominant product in all tissues; there were marked tissue differences in the relative amounts of 3-methyladenine. In bone marrow, 3-methyladenine ranged from 27-40%, in the spleen from 22-29%, and in thymus from 16-19%. 6-Methoxyguanine ranged in relative proportion from 2-5% in tissues of rats given 50 mg/kg methylnitrosourea and from 4-8% in tissues of rats given 60 mg/kg. 3-Methyladenine was present in unusually large amounts in tissues thought to play a role in the genesis of thymic lymphomas.

- 0360 CARCINOGENESIS IN TISSUE CULTURE: XIII. BINDING OF 4-NITROQUINOLINE 1-OXIDE- $^3\text{H}$  TO NUCLEIC ACIDS AND PROTEINS OF L.P3 AND JTC-25.P3 CELLS. (E.) Andoh, T. (Inst. Med. Sci., U. Tokyo, Japan), K. Kato, T. Takaoka and H. Katsuta. *Int J Cancer* 7(3):455-467, 1971.

Mouse fibroblast cell cultures were treated with  $^3\text{H}$ -labeled 4-nitroquinoline 1-oxide (4-NQO); the effect of the carcinogen on cell population, and the binding of the carcinogen to macromolecular molecules were observed. When 4-NQO was added to cultures in concentrations of  $1 \times 10^{-6}$  M, cell proliferation accelerated whereas at a concentration greater than  $5 \times 10^{-6}$  growth inhibition or cell destruction were exhibited in cultures with population densities of  $10^5$  cells/culture tube. However, when cultures with higher cell populations ( $4 \times 10^5$  cells/culture tube) were treated, a lower rate of inhibition was observed at the same concentrations. In this case no growth acceleration was found. Population-dependent growth inhibition by 4-NQO was thought to be due to population-dependent incorporation of 4-NQO into cells. Labeled 4-NQO was added to the perchloric acid (PCA)-soluble and to the PCA-precipitable fractions of mouse fibroblasts. Uptake of label in the PCA-soluble fraction reached a maximum of 434,777 dpm of  $^3\text{H}$  label/culture flask within 30 min, but the label was gradually released; by 5 hr after 4-NQO treatment, the uptake of label had declined to 1000



dpm/flask. When labeled 4-NQO was added to the PCA-precipitable fraction of fibroblasts, label uptake again reached its maximum within 30 min (4,000 dpm/flask); however cells of the acid-precipitable fraction retained the label for a longer time than did cells of the acid-soluble fraction. By 5 hr after carcinogen treatment, cells of the acid-precipitable fraction showed an uptake of 4,000 dpm/flask, and the uptake did not begin to decline until about 7 hr after 4-NQO treatment. Labeled 4-NQO was found to bind uniformly to every fraction of the soluble proteins of the fibroblasts; the radioactivity ratio of the fibroblast nucleic acid fraction to fibroblast protein fraction was 1:3. Labeled 4-NQO also bound to tRNA, DNA and rRNA.

- 0361 INTERACTION OF A CARCINOGEN, 4-NITROQUINOLINE-1-OXIDE, WITH NUCLEIC ACIDS: CHEMICAL DEGRADATION OF THE ADDUCTS. (E.) Tada, M. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan) and M. Tada. *Chem Biol Interact* 3(3):225-229, 1971.

Rat ascites hepatoma cells were exposed to tritium-labeled 4-nitroquinoline-1-oxide (4NQO) and the carcinogen-nucleic acid adducts were investigated. RNA and DNA isolated from  $^3\text{H}$ -4NQO cells bound 1-2 molecules of 4-NQO/ $10^4$  nucleotides. When the carcinogen-nucleic acid adducts were subjected to paper chromatography it was found that radioactivity was associated with the nucleic acids. Aqueous solutions of carcinogen-nucleic acid adducts were heated, releasing about 40% of the carcinogen from the nucleic acid; the nature of the released compound was examined using paper chromatography. The heat-released compound was a single component having white-blue fluorescence; it had a pH-fluorescence titration curve identical with that of 4-aminoquinoline-1-oxide (4-AQO). Thin layer chromatography also suggested that the released compound was 4-AQO. It was concluded that the quinoline derivative bound to nucleic acids was split off by alkali as 4-AQO. 4-AQO was among the degradation products seen when the RNA adduct was treated with 1 N HCl at 100°; acid degeneration of the DNA adduct also produced 4-AQO.

- 0362 PULMONARY ADENOMA IN URETHAN-TREATED SWISS MICE: IX. DEVELOPMENT OF ADENOMAS IN BABY MICE NURSED BY URETHAN-TREATED MOTHERS. (Fr.) Adenis, L. (Inst. Cancer Res., Lille, France), M. N. Vlaeminck and J. Driessens. *C R Soc Biol* 164(12):2526-2528, 1971.

Urethan carcinogenicity in young mice nursed by urethan-treated mothers during the lactating period was investigated. Seven Swiss mice that gave birth to 35 babies received 12 i.p. injections of 0.1 ml of a 6% urethan solution on alternate days starting from the day of delivery. All 31 surviving young mice developed pulmonary tumors 8 months later. The average number of tumors per animal was 9.3. Spontaneous tumor incidence was approximately 25% with an average of 2 tumors per control animal. It appears that the parenterally administered carcinogen undergoes partial excretion via the lactating mammary gland; however, the high susceptibility of newborn Swiss mice to urethan carcinogenicity is emphasized.

- 0363 STUDIES ON ACUTE METHIONINE TOXICITY: I. NUCLEOLAR DISAGGREGATION IN GUINEA PIG HEPATIC CELLS WITH METHIONINE OR ETHIONINE AND ITS REVERSAL WITH ADENINE. (E.) Shinozuka, H. (Temple U. Sch. Med., Philadelphia, Pa.), L. W. Estes and E. Farber. *Amer J Path* 64(2):241-249, 1971.

The effects of methionine and ethionine on the fine structure of hepatic cell nucleoli of guinea pigs and rats were investigated. Guinea pigs were given a single i.p. injection of L-methionine in a dose of 0.5 or 1.0 mg/g of body wt. Two hours after methionine was injected the majority of the hepatic parenchymal cells began to lose their compact structure and showed disruption of nucleolonema. By 4 hr, almost all the hepatic parenchymal cells appeared with severe nucleolar changes. Nucleoli showed complete fragmentation. Large aggregates of interchromatinic granules and condensation of chromatin appeared in the nucleoplasm. These changes were quite similar to the lesions induced by ethionine in the liver of the rat or guinea pig. The methionine-induced nuclear and nucleolar lesions persisted up to 10 hr after the injection. When guinea pigs were given adenine sulfate 4 hr after the methionine injection a reversal of the nucleolar lesions occurred. Four hr after adenine was injected many nucleoli no longer had signs of fragmentation. The nuclei of many hepatic cells contained multiple small nucleoli consisting of granular and fibrillar components of normal nucleoli. Some of these simple nucleoli showed a twisted rope-like structure with a constant width of 0.5  $\mu$  and with varying lengths. Some nucleoli showed an apparent fusion of simplified forms and some showed almost complete recovery. Injecting methionine into rats induced no nucleolar abnormalities. It is suggested that the mechanism of nucleolar fragmentation induced by methionine or ethionine is related to the accumulation of S-adenosyl compounds with concomitant ATP deficiency in the liver.

- 0364 MIXED-FUNCTION OXIDATION IN TUMORS. (E.) Brown, H. D. (Cancer Res. Ctr., Columbia, Mo.), S. K. Chattopadhyay, S. N. Pennington, J. S. Spratt and H. P. Morris. *Brit J Cancer* 25(1):135-141, 1971.

The activity of enzymes believed to be related to the electron flow chain at the level of NADPH, ferricyanide reduction, cytochrome P-450 and substrate hydroxylation was assayed in liver microsomes of normal, tumor-bearing and X-irradiated rats. NADPH oxidase, NADPH-ferricyanide reductase and benzo(a)pyrene hydroxylase were reduced 45%, 42% and 38%, resp., in livers of breast-tumor-bearing rats as compared with livers of normal rats. Cytochrome P-450 and cytochrome  $b_5$  were also at lower levels in livers of tumor-bearing rats than in normal liver. Liver microsomes from lactating rats were intermediate in value between those of non-lactating normal rat liver and tumor-bearing rat liver for NADPH oxidase, NADPH ferricyanide reductase and cytochromes P-450 and  $b_5$ . Cyto-



chrome P-450 and cytochrome b<sub>5</sub> were absent from mammary tissue. Normal liver, kidney, lung and colonic tissue contained more benzo(a)pyrene hydroxylase activity than tissues of tumor-bearing rats. Enzymes in liver microsomes of rats bearing Morris hepatoma 7777 were compared with enzymes in normal rat liver. NADPH oxidase levels were similar in both groups. Morris hepatoma 7777-bearing rat liver, however, showed markedly reduced levels of NADPH-ferricyanide reductase and cytochrome P-450 by comparison to normal rat liver. Benzo(a)pyrene hydroxylase was lower in hepatoma-bearing rat liver than in normal rat liver. Rats given whole-body X-irradiation showed increased cytochrome P-450 and NADPH oxidase activity as compared to unirradiated rats; the amounts of enzyme in the livers of irradiated rats was correlated positively with the dose of radiation.

0365 ENDOCERVICAL EFFECTS OF ORAL CONTRACEPTIVES. (Hun.) Vago, J. (Trnacs Bugat Pal Hosp., Gyongyos Varos, Hungary) and J. Simarski. *Magy Onkol* 15(2):104-109, 1971.

0366 EFFECTS OF CARCINOGENIC NAPHTHALENE DERIVATIVES ON SOME ENZYME ACTIVITIES. (Rus.) Soloimskaya, Y. (No affiliation). *Vop Onkol* 14(4):98-99, 1971.

0367 AGE-DETERMINED SUSCEPTIBILITY OF MOUSE EMBRYOS TO URETHAN CARCINOGENICITY. (Rus.) Kolesnichenko, T. S. (Acad. Med. Sci., Moscow, U.S.S.R.) and T. V. Nikonova. *Biull Eksp Biol Med* 71(4):85-87, 1971.

0368 FORMATION OF BENZO(a)PYRENE IN THE PROCESS OF PETROLEUM EXTRACTION. (Rus.) Kolyadich, M. N. (Inst. Work Hyg. Occup. Dis., Moscow, U.S.S.R.), A. Y. Khesina, S. S. Shefer and V. P. Yamskova. *Gig Tr Prof Zabol* 15(5):3-6, 1971.

0369 STUDIES OF POLYCYCLIC HYDROCARBON HYDROXYLASES OF THE INTESTINE POSSIBLY RELATED TO CANCER: EFFECT OF DIET ON BENZOPYRENE HYDROXYLASE ACTIVITY. (E.) Wattenberg, L. W. (U. Minnesota Med. Sch., Minneapolis). *Cancer* 28(1):99-102, 1971.

0370 UNMASKING OF PROTEINS BY *IN VITRO* METHYLATION OF RAT LIVER RNA DURING AZO DYE CARCINOGENESIS. (E.) Briere, N. (Fac. Med., U. Sherbrooke, Quebec, Canada). *Stain Techn* 46(4):201-206, 1971.

0371 CHANGES IN MOUSE LIVER RNA INDUCED BY ETHYL CARBAMATE (URETHANE) AND METHYL CARBAMATE. (E.) Williams, K. (Royal Cancer Hosp., London, England), W. Kunz, K. Petersen and B. Schnieders. *Z Krebsforsch* 76(1):62-82, 1971.

0372 ENZYMIC N-ACETYLATION OF N-HYDROXY-2-AMINOFLUORENE BY LIVER CYTOSOL FROM VARIOUS SPECIES. (E.) Lotlikar, P. D. (Temple U. Sch. Med., Philadelphia, Pa.) and L. Luha. *Biochem J* 123(2):287-289, 1971.

0373 THE ACTION OF AFLATOXIN B<sub>1</sub> ON *PARAMECIUM CAUDATUM* AND *PARAMECIUM BURASARIA*. (Ger.) Reiss, J. *Arch Hyg* 154(5):533-536, 1971.

0374 THE EFFECT OF PARTIAL HEPATECTOMY ON DIETHYLNITROSAMINE-INDUCED LIVER CARCINOGENESIS IN RATS. (Sp.) Morentin de, Y. M. (Navarra U., Spain) and F. Hernandez. *Rev Med Univ Navarra* 14(103):103-122, 1970.

0375 THE EFFECTS OF CHLORMADINONE AND MESTRANOL ON THE FORMATION OF MAMMARY TUMORS IN SPRAGUE-DAWLEY RATS. (E.) Rieche, K. (German Acad. Sci., Berlin). *Rev Europ Etud Clin Biol* 16:458-462, 1971.

0376 PROMOTION OF AFLATOXIN-INDUCED HEPATOMA GROWTH IN TROUT BY METHYL MALVALATE AND STERCULATE. (E.) Lee, D. J. (Dept. Food Sci., Oregon State U., Corvallis), J. H. Wales and R. O. Sinnhuber. *Cancer Res* 31(7):96-963, 1971.

0377 TEST FOR CARCINOGENIC ACTIVITY OF BENZOQUINONES IN LONG-EVANS RATS. (E.) Shimkin, M. B. (Temple U. Sch. Med., Philadelphia, Pa.), M. Gruenstein and D. R. Meranze. *Cancer Res* 31(7):957-959, 1971.

0378 SYNTHESIS OF NITROSOPIPERIDINE FROM NITRATE AND PIPERIDINE IN THE GASTRO-INTESTINAL TRACT OF THE RAT. (E.) Alam, B. S. (Harvard Med. Sch., Boston, Mass.), I. B. Saporoschetz and S. S. Epstein. *Nature* 232(5307):199-200, 1971.

0379 SYNERGISTIC EFFECT OF MUTAGENS AND INCORPORATED DNA *IN VITRO*: ANALOGY FOR BUCCOPHARYNGEAL CAVITY. (E.) Roth, D. (New York U. Med. Ctr., N. Y.) and A. Oppenheim. *Arch Environ Health* 22(4):482-486, 1971.

0380 EXPERIMENTAL MALIGNANT TUMORS IN A PERIPHERAL NERVE. (Sp.) Estable-Puig, J. F. (No affiliation) and R. F. de Estable-Puig. *Arch Fund Roux Oeefa* 4(5):5-20, 1970.

- 0381 SMOKING, CHRONIC BRONCHITIS, AND LUNG CANCER. (E.) Rimington, J. (St. Thomas' Hosp., Stockport, England). *Brit Med J* 2(5758):373-375, 1971.
- 0382 ACTION OF THE CARCINOGEN 7-BROMOMETHYLBENZ(a)ANTHRACENE ON SYNTHETIC POLYNUCLEOTIDES. (E.) Pochon, F. (Biol. Phys.-Chem. Inst., Paris, France) and A. M. Michelson. *Europ J Biochem* 21(1):144-153, 1971.
- 0383 *IN VITRO* INDUCTION OF VEGETATIVE BUDS BY TOBACCO SMOKE CONDENSATE. (E.) Kochhar, T. S. (Dept. Botany, U. Kentucky, Lexington), P. R. Bhalla and P. S. Sabharwal. *Experientia* 27(5):591-592, 1971.
- 0384 INTOLERANCE OF TOBACCO IN PATIENTS WITH GASTRIC CANCER. (E.) Zacho, A. (Finsen Inst., Copenhagen, Denmark), J. Nielsen, V. Larsen and C. Cederqvist. *Acta Chir Scand* 137(3):277-278, 1971.
- 0385 POSSIBLE BIOLOGICAL IMPORTANCE OF FIBRE DIAMETERS OF SOUTH AFRICAN AMPHIBOLES. (E.) Timbrell, V. (Llandough Hosp., Penarth, Glamorgan, Wales), D. M. Griffiths and F. D. Pooley. *Nature* 232(5305):55-56, 1971.
- 0386 ASBESTOS AND MESOTHELIOMA IN MAN. (E.) Harington, J. S. (South African Inst. Med. Res., Johannesburg), J. C. Gilson and J. C. Wagner. *Nature* 232(5305):54-55, 1971.
- 0387 CARCINOGENIC NITROGEN COMPOUNDS: PART LXX. POLYCYCLIC NAPHTHYRIDINES BY MEANS OF THE ULLMANN-FETVADJIAN REACTION. (E.) Kuu-Hoi, N. P. (Inst. Chem. Natural Substances, Gif-sur-Yvette France), P. Jacquignon and M. Mangane. *J Chem Soc (Org)* 10:1991-1993, 1971.
- 0388 INTERACTION OF THE CARCINOGEN N-ACETOXY-N-2-ACETYLAMINOFLUORENE WITH POLYADENYLIC ACID: DEPENDENCE OF REACTIVITY ON CONFORMATION. (E.) Kriek, E. (Netherlands Cancer Inst., Amsterdam) and J. Reitsema. *Chem Biol Interact* 3:397-400, 1971.
- See also:
- \* (Rev): 0302, 0303, 0304, 0305, 0310, 0320, 0333
  - \* (Immun): 0459, 0488
  - \* (Path): 0507
  - \* (Epid-Biom): 0511, 0524, 0534



# PHYSICAL CARCINOGENESIS

0389 CYTOGENETIC INVESTIGATION OF INDUSTRIAL WORKERS OCCUPATIONALLY EXPOSED TO GAMMA RAYS. (E.) Popescu, H. I. (Inst. Hyg. Pub. Hlth., Bucharest, Romania) and D. T. Stephanescu. *Radiat Res* 47(2):562-570, 1971.

Karyotype studies were performed on blood cells from industrial workers exposed to excessive and permissible amounts of cobalt and iridium gamma radiation. Eight workers in the group exposed to permissible radiation sustained doses ranging from 140-6,820 mrad over periods ranging from 5-17 yr. Eight workers in the group exposed to excessive radiation levels sustained doses ranging from 21-14,980 mrad over periods ranging from 0.6-14 yr. Persons exposed to radiation and persons not exposed to any radiation (controls) showed similar frequencies of aneuploid blood cells and similar incidences of chromatid breaks in blood cell chromosomes. Two chromosomal fragments were found in 1600 blood cell karyotypes taken from controls. Chromosomal aberrations recorded in irradiated subjects included 54 fragments, 3 dicentrics, 1 abnormally long chromosome and 3 quadriradials. The difference between the incidence of chromosomal aberrations in controls and in persons exposed to radiation was found to be statistically significant. Chromosomal aberrations in persons exposed to permissible doses of radiation included 16 fragments and 1 quadriradial; aberrations in persons exposed to excessive amounts of radiation included 38 chromosomal fragments, 3 dicentrics, 1 abnormal monocentric and 2 quadriradials. The difference between the incidence of fragments in the 2 groups of exposed workers was statistically significant.

0390 FIVE-YEAR FOLLOW-UP OF PRIMATES EXPOSED TO 55 Mev PROTONS. (E.) Traynor, J. E. (U.S. Air Force Sch. Aerospace Med., Brooks AFB, Texas) and H. W. Casey. *Radiat Res* 47(1):143-148, 1971.

0391 X-RAY-INDUCED CHROMOSOMAL ALTERATIONS IN THE NORMAL KARYOTYPE RAT. (Sp.) Orduz, M.G.B. (Nat'l. Cancer Inst. Bogota, Colombia) J. E. B. Villegars, H. G. Estrada, F. J. H. Perez, F. R. Pardo. *Univ Med* 13(2):123-134, 1971.

0392 PERITONEAL FLUID CYTOLOGY IN IRRADIATION-INDUCED OVARIAN TUMORS OF MICE. (E.) McGowan, L. (George Washington U. Med. Ctr., Washington, D. C.) and R. H. Davis. *Obstet Gynec* 38(1):125-135, 1971.

0393 VESICAL NEOPLASMS OCCURRING AFTER RADIATION TREATMENT FOR CARCINOMA OF THE UTERINE CERVIX. (E.) McIntyre, D. (Christie Hosp., Manchester, England) and R. C. S. Pointon. *J Roy Coll Surg Edinb* 16(3):141-146, 1971.

0394 THYROID FUNCTION IN ANIMALS EXPOSED TO REPEATED SMALL DOSES OF IONIZING RADIATION. (Pol.) Denisiewicz, R. (Acad. Med., Warsaw, Poland), Z. Maziarz and M. Dworakowski. *Acta Physiol Pol* 22(3):351-360, 1971.

See also:

- \* (Rev): 0331, 0332, 0334
- \* (Immun): 0472
- \* (Epid-Biom): 0523

- 0395 ISOLATION OF A POLYOMA-NUCLEOPROTEIN COMPLEX FROM INFECTED MOUSE-CELL CULTURES. (E.) Green, M. H. (Dept. Biol., U. California, San Diego), H. I. Miller and S. Hendler. *Proc Nat Acad Sci USA* 68(5):1032-1036, 1971.

A complex of viral DNA and protein was extracted from mouse cells infected with polyoma virus by Triton extraction of whole cells or by extraction of the DNA-protein complex from the nuclei of infected cells without the use of detergent. Extraction with Triton yielded a homogeneous rapidly sedimenting material labeled with tritiated thymidine. Polyoma virus DNA from infected mouse cells was found on centrifugation to sediment in a single peak at about 55S. Fast-sedimenting,  $^3\text{H}$ -labeled polyoma DNA-protein complex material was examined by sedimentation in alkaline sucrose gradients; 75% of labeled DNA sedimented as covalently-closed circular polyoma DNA. When the polyoma DNA-protein complex, extracted from infected mouse cells by the nuclear extraction procedure, was labeled for 5 min with  $^3\text{H}$ -thymidine and subjected to centrifugation in neutral sucrose gradients, it was found that 5 min-labeled DNA sedimented more slowly than did labeled DNA isolated from cells labeled with  $^3\text{H}$ -thymidine for 30 min. Five min-labeled DNA was found to be nicked in one or both of its strands. Neither the Triton extraction method nor the nuclear extraction method yielded free DNA from polyoma virus-infected mouse cells. The present results support the hypothesis that most of the replicating and newly replicated polyoma DNA is associated with a discrete amount of protein in mouse cells.

- 0396 POSSIBLE CLONAL ORIGIN OF COMMON WARTS (*Verruca vulgaris*). (E.) Murray, R. F. (Howard U. Coll. Med., Washington D.C.), J. Hobbs and B. Payne. *Nature* 232(5305):51-52, 1971.

Blood was taken from 12 Negro females and tested by electrophoresis for glucose-6-phosphate dehydrogenase (G6PD); it was found that 6 of the 12 subjects were heterozygous for G6PD. In addition, warts (*Verruca vulgaris*) were removed from the skin of the subjects and the G6PD phenotype of wart tissue was determined (the 2 possible phenotypes for wart tissue G6PD were designated A+ and B+). In 2 of the 6 heterozygotes the phenotype of wart tissue was A+ only and in 4 the phenotype was B+ only; blood in the other 6 patients showed only a single phenotype and in these patients wart tissue had the same phenotype as blood. The finding that wart tissue from individuals heterozygous for G6PD showed only 1 G6PD phenotype in each case indicated that warts are of clonal origin. It was suggested that the verrucal virus infects groups of cells having the same G6PD phenotype, or that it infects a single cell.

- 0397 SENSITIVITY OF DOMESTIC RABBIT CELL LINES, DERIVED FROM NORMAL OR INFECTED SKIN OR FROM SHOPE PAPILLOMA VIRUS-INDUCED TUMORS, TO ANIMAL VIRUSES. (Fr.) Chardonnet, Y. (C.N.R.S., Paris, France), L. Barrilliot and R. Sohier. *Ann Inst Pasteur (Paris)* 121(1):119-136, 1971.

The sensitivity of 9 rabbit cell lines (4 diploid derived from normal adult skin, 2 heteroploid derived from normal kidney and normal cornea, 1 pseudodiploid derived from skin previously infected with Shope papilloma virus, 1 pseudodiploid derived from an 80 days-old papilloma and one derived from a Shope papilloma virus-induced carcinoma) to animal viruses was investigated. Herpes simplex virus and Shope fibroma virus were reported able to multiply through 7 passages of each cell line derived from normal rabbit skin tissue or from skin infected with Shope papilloma virus 24 hr before the test. Multiplication of each of these 2 viruses was discontinued at either the 2nd or 3rd passage when inoculated cell lines derived from Shope papilloma virus induced benign or malignant tumors. Neither adenovirus 7, nor Shope papilloma virus, nor ECHO virus 4, nor ECHO virus 11 produced microscopically detectable alterations in cell lines derived from investigated rabbit tissue.

- 0398 PAPOVA-LIKE VIRUS PARTICLES IN A HUMAN BRAIN TUMOR. (E.) Bastian, F. O. (Duke U. Med. Ctr., Durham, N.C.). *Lab Invest* 25(2):169-175, 1971.

Tissue from a choroid papilloma located in the fourth ventricle of a 33-yr-old woman was examined under the electron microscope. Epithelial cells of the papilloma and of normal choroid plexus were similar morphologically. Tumor epithelial cells, but not normal epithelial cells, contained electron-dense particles with spherical to pentagonal shapes. Particles varied in size from 33-43.5 m $\mu$ . Most particles are aggregated either singly or in clusters throughout the cytoplasmic matrix and within the dilated endoplasmic reticulum of tumor cells. These particles had the morphologic features of viruses of the papova group.

- 0399 CHROMOSOMAL VARIABILITY IN TEN CLONED SUBLINES OF NEWLY ESTABLISHED BURKITT'S LYMPHOMA CELL LINE. (E.) Ikeuchi, T. (Roswell Park Mem. Inst., Buffalo, N.Y.), J. Minowada and A. A. Sandberg. *Cancer* 28(2):499-512, 1971.

Karyotype studies were performed on the parental cell line and on 10 cloned cell lines taken from a biopsy specimen of Burkitt's lymphoma. In the parental line the distribution of chromosome numbers had a sharp mode at 46 and the frequency of polyploid cells was low (3.3% and 3.7% in 2 tests). Parental cells showed 2 marker chromosomes: a B-group chromosome with an elongated short arm, designated M<sub>B</sub>, and a G-group chromosome with a partially deleted long arm, designated M<sub>G</sub>. Almost all parental cell metaphase cells showed the M<sub>B</sub> marker, and 74% of parental cell metaphases contained the M<sub>G</sub> marker. Twenty-two percent of parental cell metaphases showed centromeric attenuation of one or both the E16 chromosomes. Of the 10 cloned sublines of the



parental cells, 5 had additional modes of chromosome numbers at 45 or 47; the frequency of polyploid cells in the cloned sublines ranged from 6.2-15.8%. Karyotypic abnormalities which were absent from the parental cells were present in the cloned cells. However, all 10 of the clones showed the  $M_b$  marker in nearly 100% of cells and the  $M_g$  marker in 73-90% of cells. Three clones showed partial monosomy for the long arm of the E18 chromosome, an absence of the Y-chromosome, and a possible isochromosome of one of the D13-15 group. The parent cell line and all of the cloned sublines were positive for  $\gamma$  and  $\mu$  heavy chain and for  $\mu$  light chain immunoglobulins.

0400 BURKITT'S LYMPHOMA AND TROPICAL SPLENOmegaly SYNDROME. (E.) Ziegler, J. L. (Makerere U. Med. Sch., Kampala, Uganda). A. Z. Bluming and A. C. Templeton. *Lancet* (7719): 317, 1971.

A case of Burkitt's lymphoma in a Ugandan girl aged 10-yr-old who also presented symptoms of tropical splenomegaly syndrome was described. The patient had maxillary and orbital tumors as well as ovarian tumors; the ovarian tumors were diagnosed as Burkitt's lymphoma. In addition, the patient showed pronounced hepatosplenomegaly; sinusoidal lymphocytosis and Kupffer cell hyperplasia were observed in liver biopsy specimens. The coincidence of Burkitt's lymphoma and tropical splenomegaly syndrome in one patient was not unexpected, for there is epidemiological evidence linking the 2 conditions to malaria.

0401 CONSTANT PRODUCTION OF TYPE C VIRUS PARTICLES IN A CONTINUOUS TISSUE CULTURE DERIVED FROM PLEURAL EFFUSION CELLS OF A LYMPHOMA PATIENT. (E.) Priori, E. S. (M. D. Anderson Hosp. and Tumor Inst., Texas Med. Ctr. Houston), L. Dmochowski, B. Meyers and J. R. Wilbur. *Nature* 232(28):61-62, 1971.

Monolayer cultures of cells from pleural effusion of an American child with Burkitt's lymphoma were found to produce large numbers of virus particles in the 10th passage generation (120 days in tissue culture). The particles resembled type C particles; budding, immature and mature virus particles were found. The chromosome number of virus-producing cells was aneuploid, ranging from 60-130. Cultured pleural effusion cells included fibroblasts, giant multinucleated cells, small mononucleated cells and large epitheloid cells; all cell types produced virus particles. The particles appeared to possess a group-specific antigen different from any known animal leukemia virus group-specific antigens.

0402 BURKITT LYMPHOBLASTS AND THEIR EPSTEIN-BARR VIRUS: SYNTHESIS OF VIRAL DNA AND PROTEINS IN ARGININE DEPRIVED CELLS. (E.) Becker, Y. (Hebrew U.-Hadassah Med. Sc., Jerusalem, Israel) and A. Weinburg. *Israel J Med Sci* 7(4):561-567, 1971.

Lymphoblasts from a Burkitt's lymphoma (EB<sub>3</sub> cells)

were grown in conventional and in arginine-deprived media and the effect of arginine deprivation on macromolecular synthesis was observed. Arginine deprivation markedly inhibited RNA synthesis in EB<sub>3</sub> cells; in cells grown in conventional media, RNA synthesis at 30 hr of incubation was 3-fold what it was in arginine-deprived cell cultures. Arginine deprivation also inhibited protein synthesis in EB<sub>3</sub> cells during the G2 phase of mitosis, but it did not affect the incorporation of lysine into histones during the S phase. However, the incorporation of lysine into histones during the G2 phase was completely abolished in arginine-deprived lymphoblasts. DNA synthesis in arginine-deprived EB<sub>3</sub> cells was also inhibited; DNA synthesis in cells growing in normal media proceeded at about 2 times the rate of DNA synthesis in arginine-deprived cells. The nature of the DNA molecules synthesized by the arginine-deprived EB<sub>3</sub> cells was determined by centrifugation in cesium chloride density gradients. DNA molecules with a density of 1.719 g/cm<sup>3</sup> were found to constitute 20% of the total arginine-deprived EB<sub>3</sub> cell DNA; these molecules had the density of Epstein-Barr virus DNA. DNA of this density was seen only in EB<sub>3</sub> cells grown in arginine-deprived media. Most of the proteins synthesized by arginine-deprived EB<sub>3</sub> cells resembled the structural proteins of the herpes simplex and Epstein-Barr viruses in their electrophoretic mobility.

0403 ANTIBODY TO HUMAN CELL LINES WITH AND WITHOUT ULTRASTRUCTURAL EVIDENCE FOR EPSTEIN-BARR VIRUS (EBV) INFECTION IN SERA FROM PATIENTS WITH DIVERSE VIRAL ILLNESSES. (E.) Beltran, G. (Dept. Med., Tulane U., New Orleans, La.), J. W. Northington, E. Leiderman, W. J. Mogabgab and W. J. Stuckey. *Int J Cancer* 7(3):375-379, 1971.

Anti-Epstein-Barr virus antibody titers were determined in sera from 116 acute or convalescent patients with viral infections including herpes simplex, adenovirus T4, coxsackie A21, rhinovirus, rubella and parainfluenza virus; Epstein-Barr virus-containing EB<sub>3</sub> cells from a case of Burkitt's lymphoma were used as antigens in immunofluorescence tests for virus antibody. Sera from 23 patients with *Mycoplasma pneumoniae* infections were also tested. Anti-Epstein-Barr virus antibody was found in 125 of the total of 139 sera tested; only in 16 cases was the antibody titer greater than 1:80. Antibody titers in sera from convalescent patients were higher than titers in sera from the paired acute patients in 1 case only; in 5 cases titers of antibody in the convalescent sera were lower than in the acute sera and in the remainder, antibody titers were similar in convalescent and in acute sera. In a related experiment, 31 sera containing antibodies against the EB-3 cells were tested for antibodies against cells taken from leukemic patients (TU cells). None of the 31 sera showed a positive reaction to the TU cell antigens. This finding indicated that there was no antigenic relation between Epstein-Barr virus and a characteristic tubular structure found in the TU cells.

- 0404 RIBOSOMAL RNA IN AVIAN LEUKOSIS VIRUS PARTICLES. (E.) Obara, T. (Max-Planck Inst. Virus Res., Tubingen, Germany), D. P. Bolognesi and H. Bauer. *Int J Cancer* 7(3):535-546, 1971.

Viral RNA was extracted from the plasma cells of leukemic chickens infected with avian myeloblastosis virus and from tissue culture fluid of myeloblastosis-associated virus; sucrose gradient centrifugation of virus RNA revealed 3 major bands with optical densities of 0.4, 1.0 and 0.75 (260 mμ). Most of the RNA was concentrated in the band with optical density 1.0. In continuous flow spectrophotometry tests, viral RNA was found to consist of 5 components with sedimentation constants of 62 s, 27 s, 17 s, 9 s and 4-5 s. The estimated molecular weights of the 62 s, 27 s and 17 s components were  $8.9 \times 10^6$  daltons,  $1.6 \times 10^6$  daltons and  $6.0 \times 10^5$  daltons, resp. The 27 s and 17 s components of the viral RNA were found to have electrophoretic and sedimentation properties similar to those of ribosomal RNA. Base ratio analysis and hybridization experiments further confirmed the hypothesis that these components of the viral RNA were ribosomal in origin.

- 0405 A TRANSMISSIBLE FELINE FIBROSARCOMA OF VIRAL ORIGIN. (E.) McDonough, S. K. (U. Pennsylvania Sch. Veterinary Med., Philadelphia), S. Larsen, R. S. Brodey, N. D. Stock and W. D. Hardy, Jr. *Cancer Res* 31(7):953-956, 1971.

A fibrosarcoma which developed spontaneously on the thigh of a female cat was examined under the electron microscope; whole cell or cell-free preparations of this tumor were injected into 10 littermate kittens. The original tumor tissue appeared as a pleomorphic fibroblastic growth; some areas of the tumor were relatively well-differentiated, consisting of collagenous tissue, while other areas consisted of cellular anaplastic sarcomatous tissue which infiltrated surrounding muscle tissue. Multinucleated giant cells were seen, and many immature and mature budding C-type virus particles were in evidence. Fibrosarcomas developed in 8 of the 10 kittens given tumor cell inoculations. The latent period for tumor appearance ranged from 7-53 days; in 1 case, developing tumors regressed. Developing tumors were less pleomorphic than the anaplastic regions of the original tumor but less well-differentiated than the well-differentiated regions of the original tumor. C-type virus particles were seen under the electron microscope in tumor material from 2 of the 10 kittens (7 of the tumors developed by the kittens were not examined by electron microscope). Immunodiffusion studies showed extracts of the original tumor to be identical to the feline leukemia virus group-specific antigen.

- 0406 ISOLATION AND CHARACTERIZATION OF A LYMPHATIC LEUKEMIA VIRUS IN THE FRIEND VIRUS COMPLEX. (E.) Steeves, R. A. (Roswell Park Mem. Inst., Buffalo, N.Y.), R. J. Eckner, M. Bennett, E. A. Mirand and P. J. Trudel. *J Nat Cancer Inst* 46(6):1209-1217, 1971.

A lymphatic leukemia virus (LLV), indigenous to Friend virus (FV) preparations that also contain spleen focus-forming virus (SFFV), was isolated free of detectable SFFV. The SFFV was removed by 4 serial passages of FV in newborn rats, by 1 blind passage through newborn C57BL mice, or by endpoint dilution. Virtually all Swiss mice inoculated i.p. at birth with 0.1 ml of LLV developed lymphatic leukemia within 20 wk, and most mice had grossly enlarged spleens and livers within 10 wk. In Swiss mice inoculated at 4 wk of age (0.2 ml i.p.), the disease had a lower incidence (~50%), a longer latent period, a slower progression, and a greater frequency (~50%) of thymus and lymph node enlargement in leukemic mice. Early responses to LLV infection included moderate splenic enlargement, transient viremia (as detected by the ability of LLV to supply a helper function for defective SFFV), and transient depression of humoral immunity. LLV is antigenically related to a virus of similar origin (Rowson-Parr virus) and has a titer apparently exceeding that of SFFV in FV stocks. It is concluded that FV preparations contain a helper virus that induces lymphatic leukemia in the absence of SFFV.

- 0407 A MAJOR GENETIC LOCUS AFFECTING RESISTANCE TO INFECTION WITH MURINE LEUKEMIA VIRUSES: I. TISSUE CULTURE STUDIES OF NATURALLY OCCURRING VIRUSES. (E.) Pincus, T. (Nat'l. Inst. Allergy. Infect. Dis., Nat'l. Inst. Hlth., Bethesda, Md.), J. W. Hartley and W. P. Rowe. *J Exp Med* 133(6):1219-1233, 1971.

The host range of N- and B-tropic murine leukemia viruses was investigated by inoculating mouse embryo cell cultures prepared from mice of various strains with the virus sub-types; "N-tropic" viruses initiated infection 30-1000 times more efficiently on NIH Swiss embryo cells than on BALB/c cells; on the other hand, "B-tropic" viruses infected BALB/c cells more efficiently than NIH Swiss cells. Embryo cells from 16 mouse strains were inoculated either with N-tropic virus (prepared from AKR-L1 cells), or with B-tropic virus (prepared from BALB/c-S2B cells), or with a Moloney virus which infected both BALB/c and NIH Swiss cells with equal efficiency (i.e., "NB-tropic" virus). All 16 mouse cells resembled either NIH Swiss mouse or BALB/c mouse cells in showing at least 60-fold greater sensitivity to either an N-tropic or a B-tropic virus. The classification of strains of mouse cells as sensitive to N-tropic or to B-tropic virus (N-type or B-type cells) was not related to the H-2 allele make-up of the cells; the H-2<sup>b</sup>, H-2<sup>d</sup>, and H-2<sup>k</sup> alleles were represented in both N-type and B-type mouse cells. When embryo cells from F<sub>1</sub> hybrid offspring of N-type and B-type parent mice were inoculated with N-tropic or B-tropic virus it was found that the offspring were 100-fold less sensitive to either virus than parent mice; this



suggested that resistance to virus was genetically dominant in mice. The F<sub>1</sub> offspring of B-type-N-type and of N-type-B-type mouse matings were backcrossed to parental N- and B-tropic strains, and cultures from backcross embryos were inoculated with N- and B-tropic virus. Backcross embryo cells showed no segregation for sensitivity to N- or B-tropic virus; this finding suggested that a single genetic locus determines *in vitro* susceptibility of mouse cells to murine leukemia viruses.

0408 A MAJOR GENETIC LOCUS AFFECTING RESISTANCE TO INFECTION WITH MURINE LEUKEMIA VIRUSES: II. APPARENT IDENTITY TO A MAJOR LOCUS DESCRIBED FOR RESISTANCE TO FRIEND MURINE LEUKEMIA VIRUS. (E.) Pincus, T. (Natl. Inst. Allergy Infect. Dis., Natl. Inst. Hlth., Bethesda, Md.), W. P. Rowe and F. Lilly. *J Exp Med* 133(6):1234-1241, 1971.

Strains of Friend murine leukemia virus (F-MLV) having different genetically-determined infectivity for various strains of mouse cells were used to infect embryo cells of F-MLV infection-susceptible and infection-resistant mice. F-MLV was of the F-S type (an efficient infector of DBA/2 mouse cells but not of BALB/c mouse cells) or of the F-B type (an equally efficient infector of BALB/c and DBA/2 mouse cells). Infected mouse cell strains showed "N-type", "B-type" or "N-B-type" infectivity with naturally occurring murine leukemia virus; "N-type" cells were readily infected with "N-tropic" murine leukemia virus (i.e., virus which infects BALB/c mice more efficiently than NIH Swiss mice). "N-B-type" cells were readily infected by a virus which infects both NIH Swiss mice and BALB/c mice with equal efficiency. Titers of F-S F-MLV virus were 100-1000 times higher in N-type cells infected with F-S virus than in infected B-type cells. F-B F-MLV virus infected N-type cells and B-type cells with equal efficiency. This indicated that the F-S virus variant was N-tropic while the F-B virus variant was N-B-tropic. When the 2 virus variants were tested on (N x B)F<sub>1</sub> hybrid mice cells it was found that the hybrids were resistant to infection with F-S but not to F-B. F-S F-MLV infection-susceptible (Fv-1<sup>S</sup>) mouse embryo cells showed N-type sensitivity to infection with naturally occurring N-, B- or N-B-tropic viruses, while F-S infection-resistant (Fv-1<sup>R</sup>) mouse cells showed B-type sensitivity. These findings indicated that the N-B genetic locus affecting the infectivity of mouse cells by naturally occurring murine leukemia viruses is identical to the Fv-1 locus affecting infectivity of mouse cells by F-MLV.

0409 EXPRESSION OF H-2 AND MOLONEY LEUKEMIA VIRUS-DETERMINED CELL-SURFACE ANTIGENS IN SYNCHRONIZED CULTURES OF A MOUSE CELL LINE. (E.) Cikes, M. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden) and S. Frieberg, Jr. *Proc Nat Acad Sci USA* 68(3):566-569, 1971.

A line of bone marrow cells derived from a BALB/c mouse was infected with Moloney leukemia virus;

infected cells were incubated with 2 anti-H-2 antisera and 1 anti-viral antiserum. When antigens became detectable in the cultures, cells were synchronized by colcemid treatment and the production of H-2 and virus antigens by infected cells was monitored during different phases of the cell cycle by indirect immunofluorescence. Anti-H-2 antigens were produced most actively during the G<sub>1</sub> phase of the cell cycle; 55 and 100% of cells were antigen-positive for the 2 H-2 antigens during this phase. The G<sub>1</sub> phase was also the peak phase for the production of viral antigen, with 80% of cells reacting positively for this antigen during the G<sub>1</sub> phase. As cells passed into the S phase the percentage of cells positive for the H-2 antigens dropped nearly to zero and the percentage of cells positive for viral antigen dropped to about 10%. Antigen production by infected cells remained at these low levels throughout the S, G<sub>2</sub> and mitosis phases; percentages of cells reacting positively for the 3 antigens commenced to increase again as cells entered the next G<sub>1</sub> phase of the cell cycle.

0410 EFFECT OF FRIEND LEUKEMIA VIRUS AND ROWSON-PARR VIRUS ON IMMUNOLOGICAL MATURATION OF MICE. (E.) Bendinelli, M. (Inst. Microbiol., U. Pisa, Italy). *Infect Immun* 4(1): 1-5, 1971.

Mice of the BALB/c strain were inoculated within 20 hr of birth with 0.05 ml of Friend virus or Rowson-Parr virus; infected mice were then given injections of  $2.5 \times 10^8$  sheep red blood cells (SRBC) and the number of plaque-forming cells (PFC) in the spleens of infected and uninfected mice was determined. In mice not infected with viruses, the PFC response to SRBC was pronounced; by 10 days after challenge with SRBC spleens of uninfected mice contained a mean number of 371.6 PFC and by 19 days after challenge the mean number of splenic PFC in uninfected mice was 19,960. Infection with Friend virus practically abolished the PFC response, mean numbers of splenic PFC in Friend virus-infected mice 10 and 19 days after challenge with SRBC were 8.9 and 8.7, resp. The effect of Rowson-Parr virus was less drastic; mean numbers of PFC in Rowson-Parr virus-infected mouse spleens 10 and 19 days after SRBC challenge were 100 and 9,500 resp.

0411 INHIBITORS ACTING ON NUCLEIC ACID SYNTHESIS IN AN ONCOGENIC RNA VIRUS. (E.) Müller, W. E. G. (Physiol. Chem. Unit, Johannes Gutenberg U., Mainz am Rhein, Germany), R. K. Zahn, and H. J. Seidel. *Nature* 232(31):143-145, 1971.

The inhibition of RNA-dependent DNA polymerase and of DNA-dependent DNA polymerase in Rauscher murine leukemia virus was investigated. Inhibition of both polymerases approaching 100% was produced by  $10^{-4}$ - $10^{-1}$  mg/ml (log) concentrations of the following agents:



Congo red, ethidium bromide, daunomycin, acridine orange, olivomycin, chromomycin, actinomycin D, protamine and histone. Of special interest was the finding that Rauscher virus RNA/DNA polymerase could be reduced to 50% by 35 µg/ml actinomycin D; 6 µg/ml of actinomycin D produced 50% inhibition of the DNA/DNA polymerase. Heparin specifically blocked Rauscher virus RNA/DNA and DNA/DNA polymerases when administered in doses of 14-20 µg/ml. Chloroquine and mitomycin C failed to inhibit the DNA polymerases in Rauscher virus.

- 0412 HEMOGLOBIN SYNTHESIS IN MURINE VIRUS-INDUCED LEUKEMIC CELLS *IN VITRO*: STIMULATION OF ERYTHROID DIFFERENTIATION BY DIMETHYL SULFOXIDE. (E.) Friend, C. (Mount Sinai Sch. Med., City U. New York, N.Y.), W. Scher, J. G. Holland and T. Sato. *Proc Nat Acad Sci USA* 68(2):378-382, 1971.

The possibility that leukemia is a disease resulting from a block in the process of maturation of hemopoietic cells was explored. Erythroid cells from mice infected with Friend leukemia virus were established in culture and treated with dimethyl sulfoxide (DMSO) in concentrations of 0.5-5%. Cells grown in media containing 0.5 or 1% DMSO multiplied at approximately the same rate as those of the control (untreated) cultures. When the concentration was increased to 2% there was a lag in growth rate during the first 48 hr, but by the 96th hr the number of cells approximated that of controls. At a concentration of 3% DMSO, cell growth was inhibited and at 5% the compound was cytotoxic, no living cells remaining after 72 hr. Of the cells allowed to grow in medium containing 2% DMSO for 4 days, a majority of the erythroblasts had matured to normoblasts which stained benzidine-positive (B+). This was accompanied by increased synthesis of heme and hemoglobin and by a decrease in the malignancy of the cells; mice given DMSO-treated leukemic cells survived for longer periods of time than controls (56 days vs 38 days). This action of DMSO, which was reversible, may represent the derepression of leukemic cells to permit their maturation.

- 0413 HETEROGENEITY OF MURINE LEUKEMIA VIRUS *IN VITRO* DNA: DETECTION OF VIRAL DNA IN MAMMALIAN CELLS. (E.) Gelb, L. D. (Nat'l. Inst. of Allergy and Infectious Dis., Bethesda, Md.), S. A. Aaronson and M. A. Martin. *Science* 172(3990):1353-1355, 1971.

The informational content of *in vitro* double-stranded DNA synthesized in mouse cells (BALB/3T3 and NIH/3T3) and normal rat kidney by Rauscher and Kirsten murine leukemia viruses (MuLV) was examined by kinetic analysis of DNA reassociation. Two classes of double-stranded DNA were discovered which represented 25 and 100% of the viral genetic information. One class of viral DNA, which represented 85% of the MuLV DNA generated, had a molecular weight of  $5.0 \times 10^6$ ; this "small" DNA was extensively duplicated in the genomes of normal and RNA tumor-virus-containing cells. The other class of DNA, representing the remainder of total synthesized viral DNA, had a molecular weight of  $19 \times 10^6$ . It was thought that the smaller DNA represented the selective transcription of a relatively small portion of the viral DNA.

- 0414 STUDIES ON AN ONCOGENIC AVIAN ADENOVIRUS (CELO): I. BIOPHYSICAL CHARACTERIZATION. (E.) Anderson, J. P. (Baylor Coll. Med., Houston, Texas), K. J. McCormick, W. A. Stenback, A. M. El Mishad and J. J. Trentin. *Proc Soc Exp Biol Med* 137(2):399-403, 1971.

Chick embryo lethal orphan virus (CELO) from the allantoic fluids of embryonated eggs was treated with 1.0% sodium deoxycholate and 0.01% trypsin and then subjected to density gradient centrifugation in 40% rubidium chloride. Virus stock purified in this manner yielded 2-3 times as many total PFU as were present in the untreated starting material. In a density gradient, CELO virus behaved similarly to the human adenoviruses. The infectious complete virus banded at a density of 1.33-1.34 g/cm<sup>3</sup>; the incomplete particles banded at a density of 1.27-1.30 g/cm<sup>3</sup>. There were 10,000 times more PFU in the lower band than in the upper band. The highest concentrations of complement fixing and hemagglutinating activity were also found to be associated with these bands. The heat stability of the CELO virion was confirmed using purified virus particles. The stability of purified virions indicates that this property is not the result of protective substances in the suspending medium. Antigenic studies indicated that CELO virus does not contain the adenovirus group antigen.

- 0415 VARIATIONS IN IMMUNOGENICITY OF DISRUPTED CELLS PREPARED FROM AN ADENOVIRUS-7 HAMSTER TUMOR CELL LINE. (E.) Panteleakis, P. N. (Merck Inst. Therapeutic Res., West Point, Pa.), V. M. Larson, W. J. McAleer and M. R. Hilleman. *J Nat Cancer Inst* 46(6):1195-1200, 1971.

Hamsters were injected with vaccines prepared by disrupting stocks of adenovirus-7 tumor cells prior to challenge with homologous hamster tumor cells, and the degree of protection against tumor development afforded by different vaccines was observed. Vaccines prepared by disrupting tumor cell suspensions by nitrogen decompression failed to protect against homologous tumor cell challenge; by 90 days after tumor cell challenge, unvaccinated hamsters had developed tumors in 55% of cases and vaccinated hamsters had developed tumors in 70% of cases. Vaccines prepared by disruption of tumor cells in the French pressure cell similarly failed to protect tumor cell recipients; unvaccinated controls and vaccinated hamsters both developed tumors in 68% of cases by 90 days after challenge. Vaccines prepared by treating tumor cells with formaldehyde failed to protect tumor cell recipients; unvaccinated controls developed tumors in 30% of cases by 90 days after challenge, and vaccinated hamsters developed tumors in 45% of cases after 90 days. Vaccines prepared by exposing tumor cells to γ-rays protected tumor cell recipients; 10% of vaccinated hamsters developed tumors by 90 days after challenge. The basis for the differences in immunogenicity in vaccines prepared by different disruption techniques was unclear; however it was noted that nonprotective vaccines were prepared by disrupting tumor cells of varying oncogenicity, while protective vaccines were derived from highly oncogenic tumor cells. Evidently



there had been some selection among different stocks of tumor cells as a result of which some stocks remained immunogenic after disruption while others did not.

- 0416 NODULE BIOASSAY OF THE MOUSE MAMMARY TUMOR VIRUS: MODIFICATIONS AND QUANTITATIVE CONSIDERATIONS. (E.) Nandi, S. (Dept. Zool., U. California, Berkeley), S. Haslam, C. Helmich and R. I. Ritter. *J Nat Cancer Inst* 46(6):1309-1315, 1971

Extracts of mammary tissues from mammary tumor virus (M-MTV)-infected mice (strains C3H, DBA/2 and BALB/cfC3H) were injected in varying concentrations into uninfected mice; recipients were given implanted pellets of estradiol plus deoxycorticosterone 4 wk after inoculation with M-MTV. The development of mammary hyperplastic nodules in hormone-treated virus-infected recipients was observed in connection with a standard bioassay of M-MTV in infected mice. The overall mortality of hormone- and virus-treated mice ranged from 20-50%. All dilutions of mammary tissue from M-MTV-infected donors produced nodules in recipients; dilutions of  $10^{-2}$  to  $10^{-5}$  or  $10^{-6}$  resulted in no evident decrease in biologic activity. Beyond this point further dilutions resulted in a gradual or precipitous decrease in nodule incidence. In a related experiment recipient mice were inoculated with whole blood or with red blood cells from mice infected with the blood-borne variety of M-MTV (R-MTV); 1 wk after virus inoculation, recipients were given 2 pituitary isografts. Isografts were destroyed by electrocauterization 9 wk later and the incidence of mammary hyperplastic alveolar nodules was observed. MTV activity was detected in mice receiving infective red blood cells at dose levels between  $10^{-1}$  g equivalent ( $10^9$  cells) and  $10^{-3}$  or  $10^{-4}$  g equivalent ( $10^6$  or  $10^7$  cells). Mice receiving R-MTV-infected blood were given 1, 2 or 3 pituitary isografts under the kidney capsule in an attempt to reduce the mortality among test mice during the assay period. Mortality among mice used in the R-MTV assay and given 1-3 pituitary isografts was less than 2%. Nodule assay with pituitary isografts also reduced the time elapsed between infection with virus and appearance of nodules.

- 0417 MOLONEY SARCOMA VIRUS-INDUCED TUMORS IN MICE: INHIBITION OR STIMULATION BY (POLY rI)·(POLY rC). De Clercq, E. (Stanford U. Sch. Med., Stanford, Calif.) and T. C. Merigan. *Proc Soc Exp Biol Med* 137(2):590-594, 1971.

Mice of the Swiss-Webster strain were given i.p. injections of either 20 or 100  $\mu$ g of (poly rI)·(poly rC) on alternate days beginning 1 day before, and continuing to 17 days after, challenge with i.m. injections of Moloney murine sarcoma virus. The effect of (poly rI)·(poly rC) on the induction of tumors in 4-6-day-old mice and in 20-day-old mice was observed. (Poly rI)·(poly rC) reduced tumor development in 4-6-day-old mice; 12 days after virus challenge 95% of controls not given (poly rI)·(poly-

rC) had developed tumors whereas 40% of mice given 100  $\mu$ g (poly rI)·(poly rC), and 60% of mice given 20  $\mu$ g (poly rI)·(poly rC) had developed tumors. When 20-day-old mice were given (poly rI)·(poly rC) before and/or after virus challenge the development of tumors was enhanced. At 12 days after virus challenge, 60% of 20-day-old control mice not given (poly rI)·(poly rC) developed tumors, while the incidence of tumors in mice given (poly rI)·(poly rC) ranged from 80-90% on day 12. In 4-6-day-old mice given (poly rI)·(poly rC) tumors appeared later than in control mice whereas in 20-day-old mice given (poly rI)·(poly rC) tumors appeared earlier than in controls.

- 0418 HISTOCHEMISTRY OF GIANT CELLS IN TUMOURS INDUCED IN GOLDEN HAMSTERS BY MURINE SARCOMA VIRUS-HARVEY. (E.) Hallows, R. C. (Imperial Cancer Res. Fund, London, England) and F. C. Chesterman. *Int J Cancer* 7(3):507-512, 1971.

Tumors were induced in hamsters by s.c. inoculation with murine sarcoma virus (Harvey); 4 tumor types were observed: subcutaneous non-infiltrating tumors, paw tumors occurring at the limb extremities, muscle tumors infiltrating muscle but not bone, and bone-eroding tumors which infiltrated bone. The histochemical characteristics of giant cells in the different types of virus-induced tumors were investigated. Giant cells generally gave strong reactions for nucleotide-linked respiratory enzymes (e.g., NAD-H oxidase) and for acid hydrolases. Non-specific alkaline phosphatase was negative or slight in giant cells from all tumors. Subcutaneous tumor giant cells gave weak reactions for substrate-specific phosphatase (e.g., ATPase). Giant cells in muscle tumors were strongly positive for substrate-specific phosphatases, as were giant cells in bone-eroding tumors. Muscle-infiltrating tumor giant cells were usually positive for phosphorylase enzyme activity. Subcutaneous tumor giant cells showed vacuoles containing lipids; vacuoles in the giant cells in other tumors rarely contained lipids. Giant cells from all tumors contained cytoplasmic granules.

- 0419 THE FORMATION AND NATURE OF FOCI INDUCED BY A MODIFIED SARCOMA VIRUS IN HUMAN CELLS. (E.) Fischinger, P. J. (Max-Planck Inst. Virus Res., Tübingen, Germany) and C. O. Moore. *J Gen Virol* 12(1):59-63, 1971.

Human embryonic muscle-skin cells were infected with the feline leukemia virus pseudotype of murine sarcoma virus (MSV(FelLV)) and attempts were made to observe MSV(FelLV)-induced foci in the human cells. It was found that maximum focus induction was achieved when feline leukemia virus was added to MSV(FelLV)-infected human muscle-skin cell cultures. Foci induced in human cells by feline leukemia virus and by MSV(FelLV) were similar to foci induced by sarcoma virus in other species. Hyperrefractile fusiform cells and round cells were seen against a background of normal cells. Since optimal focus-formation by MSV(FelLV) in the human cells required continual supplementation with feline leukemia virus it was



thought that foci in human cells were derived by localized virus spread. When foci induced by MSV (FelLV) were tested for virus production on cat cells, it was found that all 11 observed foci produced new focus-forming units of defective MSV(FelLV) on cat cells.

- 0420 NUCLEIC ACID AND PROTEINS ISOLATED FROM A STRAIN OF MURINE SARCOMA VIRUS. (E.) Horvath, A. E. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.) and R. M. Friedman. *Proc Soc Exp Biol Med* 137(3):1075-1081, 1971.

Murine sarcoma virus (MSV-0, Moloney) was grown in tissue cultures of transformed rat cells (MSB-1). The media containing the virus particles were collected and the virus purified by sucrose density gradient ultracentrifugation. The buoyant density of the purified virus was 1.16 g/ml. The incorporation of  $^3\text{H}$ -uridine was shown to be reduced in virus preparation from cells treated with a crude rat interferon preparation, when compared to controls. In tissue cultures treated with a 1:3 dilution of interferon, the incorporation of  $^3\text{H}$ -uridine was reduced to about 35% of the control. In cells treated with a 1:10 interferon dilution a depression to 60% of the control was observed. Viral nucleic acid was extracted by the SDS-phenol method and characterized by sucrose density ultracentrifugation. A sedimentation value of 52S or 64S was obtained, depending on the reference values used. Heating the viral RNA to 80° caused it to dissociate into a major 32S and minor smaller S value species, suggesting that the larger RNA is either an aggregate of smaller 32S units, or that modifications had taken place in the secondary structure of the RNA. Pancreatic ribonuclease treatment disclosed no ribonuclease-resistant RNA in the virus or in the MSB cells. This is believed to confirm the single-stranded nature of viral RNA. Six proteins were extracted from purified MSV-0 solubilized and separated by polyacrylamide gel electrophoresis.

- 0421 ULTRASTRUCTURE OF GIANT CELLS IN TUMOURS INDUCED IN GOLDEN HAMSTERS BY MURINE SARCOMA VIRUS-HARVEY. (E.) Hallows, R. C. (Imperial Cancer Res. Fund, London, England) and F. C. Chesterman. *Int J Cancer* 7(3):513-525, 1971.

Tumors were induced in hamsters by s.c. injection of Harvey murine sarcoma virus; tumors of 4 types developed: subcutaneous tumors which did not infiltrate deep tissue, paw tumors occurring at limb extremities, muscle tumors which infiltrated and destroyed striated muscle, and bone-eroding tumors which infiltrated and destroyed bone. Giant cells from tumors of each type were examined under the electron microscope. Giant cells of a "filamentous" appearance were found in subcutaneous tumors; these cells had long filamentous processes along their borders which extended between collagen bundles and sometimes enveloped adjacent lymphocytes. Nuclei in these giant cells were large and bizarre in shape. "Interlocking" giant cells were seen in all tumors; these cells had short processes interdigitating with adjacent cells. "Pleomorphic" giant cells were seen in paw, muscle and bone-eroding tumors; these cells had many nuclei and numerous short

cytoplasmic microvilli. Degenerating muscle giant cells were abundant in regions where skeletal muscle was being replaced by tumor; these cells were associated with pleomorphic giant cells. "Vegetative" muscle giant cells were occasionally seen in muscle tumors; these cells showed pseudopod-like processes. Their cytoplasm contained many tubular structures. Interdigitating cells similar to those seen in the hamster tumor giant cells have been observed in granulomas.

- 0422 MECHANISM OF ONCOGENIC TRANSFORMATION BY ROUS SARCOMA VIRUS: II. EFFECT OF RIFAMPIN ON ROUS SARCOMA VIRUS INFECTION. (E.) Richert, N. J. (U. Rochester Sch. Med. Dent., N.Y.) and P. Balduzzi. *J Virol* 8(1):62-65, 1971.

Chick embryo fibroblast cultures were infected with 100 focus-forming U/culture plate of Bryan high titer strain Rous sarcoma virus; infected cultures were treated with 50 µg/ml rifampin either on the day of virus infection, or from 1-4 days thereafter. The average number of foci of virus infection/plate in infected cultures not treated with rifampin was 73; in infected cultures treated with rifampin on days 0 or 1, the average number of foci was 57. Maximum inhibition of focus formation was seen in cultures treated with rifampin on days 1-2 after virus infection (average number of foci/plate: 18). In cultures treated with rifampin on days 2 or 3 after infection, the average number of foci/plate was 49. It appears that rifampin did not affect the formation of the provirus in infected cultures, or its transcription or translation in infected cells. Rifampin, rather, was thought to inhibit viral infection by affecting some step which occurred prior to "fixation" and activation of the virus in the host cell.

- 0423 FURTHER CHARACTERIZATION OF THE CELLULAR DNA HYBRIDIZING WITH THE RNA OF ROUS SARCOMA VIRUS. (E.) Yoshikawa-Fukada, M. (Carnegie Inst. Washington, Baltimore, Md.) and J. D. Ebert. *Proc Nat Acad Sci USA* 68(4):743-746, 1971.

Viral RNA was extracted from Rous sarcoma virus; cellular nucleic acids including DNA, ribosomal RNA and low molecular weight RNA were extracted from chick embryos. 4S and 70S viral RNA fractions were prepared by density gradient centrifugation on sucrose and competition experiments using cellular low molecular weight RNA and viral RNA were carried out. Only 10% of the hybridization between 70S viral RNA and cellular RNA was lost after competition with low molecular weight cellular RNA; when 4S viral RNA was used, as much as 40% of the hybridization was lost. The results indicated that both 70S and 4S viral RNA contained some low molecular weight cellular RNA, with the amount contained in the 4S fraction exceeding the amount contained in the 70S fraction. To examine the relationship between 70S and 4S viral RNA, competition experiments were performed with unlabeled 4S



RNA as "competitor" and  $^{32}\text{P}$ -labeled 70S and 4S RNA in the final hybrids with cellular DNA. It was found that, in the presence of low molecular weight RNA, 4S viral RNA competed significantly with 70S viral RNA; it was concluded that at least half of the 70S viral RNA which was homologous with chick-embryo DNA was also homologous with 4S viral RNA. In further hybridization experiments performed in formamide at low temperatures, the melting profiles of hybrids between 70S viral RNA and cellular DNA, and between 4S viral RNA and DNA, were similar. It was suggested that degraded 70S viral RNA and adventitious cellular DNA may each contribute to the 4S RNA present in Rous virus nucleic acid preparations.

0424 ISOZYME PATTERNS IN ROUS SARCOMA VIRUS-INDUCED TUMORS IN THE RAT. (E.)

Levan, G. (Inst. Genet., U. Lund, Lund, Sweden), F. Mitelman, W. W. Nichols, G. Beckman and L. Beckman. *Hereditas* 68(1):143-150, 1971.

Primary sarcomas were induced in rats by injecting them with Schmidt-Ruppin Rous sarcoma virus; cell cultures were established from the primary tumors and, in some cases, cultured cells from tumors were reimplanted in rats to induce tumors. The isozyme patterns of 9 enzymes were studied by electrophoresis. All primary tumors showed similar deviations from the isozyme patterns observed in normal rat connective tissue cells. Both acid and alkaline phosphatases were found to show a less intense reaction in cultured tumor cells than in tumor cells or in normal cells taken directly from rats. Amino acid naphthylamidase showed a second band on electrophoresis of some of the tumor cells; this band was missing from the electrophoretic pattern of normal cells. Tumors had a higher level of peptidase activity than did normal cells. Normal connective tissue showed esterase activity confined largely to 2 bands, while tumor tissue showed many bands of esterase. The esterase pattern in cultured tumor cells differed from that in primary tumor cells; however, on reimplantation of cultured tumor cells into rats, the electrophoretic pattern of the original primary sarcoma reappeared. Tumors showed a higher level of glucose-6-phosphatase than did normal connective tissue. Tumors and cultured tumor cells showed high levels of 6-phosphogluconate dehydrogenase; reimplanted tumor cells showed low activity levels for this enzyme in 2 of 22 cases. Tumor tissue showed a prevalence of the faster-moving bands for phosphoglucomutase activity while normal tissue showed a prevalence of the slower-moving bands for this enzyme. Different subunits of the lactate dehydrogenase enzyme were seen in tumor and normal tissue. In general, virus-induced changes in isozyme patterns were similar in all cases; when transformed cells were established in culture, the tumor isozyme pattern changed but this change was reversed by reimplanting cultured cells into recipient rats.

0425 DEOXYRIBONUCLEIC ACID POLYMERASE(S) OF ROUS SARCOMA VIRUS: EFFECTS OF VIRION-ASSOCIATED ENDONUCLEASE ON THE ENZYMATIC PRODUCT. (E.) Quintrell, N. (Dept. Microbiol., U. California, San Francisco), L. Fanshier, B. Evans, W. Levinson and J. M. Bishop. *J Virol* 8(1):17-27, 1971.

The degradation of Rous sarcoma virus RNA by an endogenous ribonuclease, and the effect of this ribonuclease on the DNA synthesized by the virus in an RNA-dependent DNA polymerase reaction, were investigated. Virions of Rous virus were found to display DNA polymerase activity only after treatment with a nonionic detergent; optimal concentrations of detergent for DNA synthesis were 0.005-0.10%. As DNA synthesis proceeded at optimal concentrations of detergent it was found that viral RNA in the reaction was degraded to an acid-soluble state; the degradation of RNA was reduced to near zero in RNA-dependent DNA synthesis reactions in which the concentration of detergent was reduced to 0.01%. The effect of detergent concentration on the nature of the enzymatic product of the RNA-dependent DNA polymerase reaction was investigated. The virion polymerase synthesized 2 classes of DNA: an initial product which cosedimented with 70S viral RNA in sucrose density gradients and a secondary product which sedimented more slowly (4-10S sedimentation velocity). Detergent concentrations which permitted optimal DNA synthesis in the RNA-dependent DNA polymerase reaction lead to disappearance of the 70S polymerase product within 1 hr after initiation of the reaction; this disappearance of the 70S DNA was ascribed to the activation of the virion-associated ribonuclease, which degraded the RNA template in the reaction. At concentrations of detergent below those optimal for DNA synthesis, the 70S enzymatic product of the DNA polymerase persisted for up to 2 hr after initiation of the reaction. It was thought that the ribonuclease which attacked the viral genome after disruption with detergent was either a surface constituent of the virus or an adsorbed contaminant.

0426 PROPERTIES OF A SOLUBLE DNA POLYMERASE ISOLATED FROM ROUS SARCOMA VIRUS. (E.) Duesberg, P. (Dept. Molec. Biol., U. California, Berkeley), K. V. D. Helm and E. Canaani. *Proc Nat Acad Sci USA* 68(4):747-751, 1971.

The DNA polymerase of the Prague strain of Rous sarcoma virus (PR RSV) and of the Schmidt-Ruppin strain was solubilized by incubation with buffered glycerol in disruption buffer containing Triton X-100. The enzyme was examined by DEAE-cellulose chromatography, and it was found that 80% of the  $^{14}\text{C}$ -labeled viral protein applied to the cellulose column was recovered from the column; this finding indicated that PR RSV DNA polymerase made up at most 2% of the soluble protein of the virus. Before incubation with pancreatic RNase, the sedimentation coefficient was 8S, while following incubation with RNase the sedimentation coefficient of the polymerase was re-

duced to 6S. The recovery of DNA polymerase activity after sucrose gradient centrifugation was 80% without RNase treatment and 40-80% with RNase treatment. Electrophoretic analysis of the 6S component of the DNA polymerase indicated that this fraction of the enzyme differed from 90% of the viral glycoprotein; the 10% portion of the viral glycoprotein which could not be separated from the 6S DNA polymerase had the same electrophoretic distribution as the 2 known viral glycoproteins. In tests designed to establish whether the DNA polymerase of PR RSV was able to use template RNA from various species it was found that the viral DNA polymerase was highly active with 60-70S viral RNA from PR RSV and with salmon DNA. PR RSV DNA polymerase was less active with heat-dissociated viral 60-70S RNA and with tobacco mosaic virus RNA. Neither the 8S nor the 6S PR RSV DNA polymerase had endogenous template activity. RNA-dependent and DNA-dependent DNA polymerase activities in PR RSV were thought to be mediated by the same enzyme system.

0427 INDUCTION OF MITOCHONDRIAL DNA SYNTHESIS IN MONKEY CELLS INFECTED WITH SIMIAN VIRUS 40 AND (OR) TREATED WITH CALF SERUM. (E.) Levine, A. J. (Dept. Biochem., Princeton U., N.J.) *Proc Nat Acad Sci USA* 68(4):717-720, 1971.

Confluent monolayer cultures of African green monkey kidney cells (AGMK) were infected with SV40 (200-250 plaque-forming U/cell) and the synthesis of mitochondrial and nuclear DNA in infected cells was measured by the uptake of  $^3\text{H}$ -thymidine in infected cells. Sucrose gradient sedimentation analysis of mitochondrial DNA from uninfected AGMK cells showed that uninfected cells incorporated 1000 cpm  $^3\text{H}$ -thymidine; AGMK cells stimulated with calf serum incorporated 3000 cpm  $^3\text{H}$ -thymidine. AGMK cells infected with SV40 incorporated 2000 cpm  $^3\text{H}$ -thymidine, reflecting a 2-fold increase in mitochondrial DNA synthesis in infected cultures over uninfected cultures. Synthesis of total amounts of nuclear and cytoplasmic DNA by serum-stimulated and SV40-infected AGMK cells was also measured. Calf serum induction of AGMK cells produced a 2-fold increase in mitochondrial and a 2.3-fold increase in nuclear DNA; SV40 infection of AGMK cells resulted in a 2-fold increase in nuclear DNA and a 1.7-fold increase in mitochondrial DNA. SV40 infection of mouse 3T3 cells also enhanced nuclear and mitochondrial DNA synthesis; however, SV40 infection of BSC-1 monkey cells did not result in enhanced nuclear or mitochondrial synthesis.

0428 INITIAL STAGE OF TRANSFORMATION OF PERMISSIVE CELLS BY SIMIAN VIRUS 40: DEVELOPMENT OF RESISTANCE TO PRODUCTIVE INFECTION. (E.) Hahn, E. C. (German Cancer Res. Ctr., Heidelberg) and G. Sauer. *J Virol* 8(1):7-16, 1971.

CV-1 and AGMK monkey cells were exposed to SV40; by 1 wk postinfection, cell colonies were found which

were resistant to lytic infection. SV40 tumor antigen was detected in all CV-1 cells in resistant colonies. Resistant colonies survived superinfection with SV40. To determine the conditions leading to formation of resistant colonies, CV-1 cells were infected with SV40 and the number of surviving colonies was determined 2 wk later; the yield of resistant colonies increased inversely as a function of the number of cells in the infected population. The yield of resistant colonies was found to depend on the extent to which cells were allowed to divide after infection; the largest number of resistant colonies was obtained when cells had undergone at least 3 divisions, while few if any resistant colonies were found when cells were prevented from dividing after SV40 infection. In a related experiment, high yields of resistant colonies were obtained when contact-inhibited SV40-infected cells were released from contact inhibition 10-14 hr after infection. When growing AGMK cells infected with SV40 were reseeded on confluent monolayers, reseeded cultures produced only 5% of the number of resistant colonies produced by infected AGMK cells not reseeded on confluent monolayers. Infection of monkey cells with large numbers of SV40 reduced the survival of cells; at multiplicities of infection (MOI) greater than 5, survival was an inverse function of MOI. However, some resistant colonies were found in cultures infected at MOI = 50. Exposure of infective SV40 to UV for up to 2 min increased the number of resistant colonies by 400%; irradiation of SV40 for a longer period (to 6 min) reduced the yield of resistant colonies.

0429 SERUM FACTOR REQUIREMENTS OF NORMAL AND SIMIAN VIRUS 40-TRANSFORMED 3T3 MOUSE FIBROBLASTS. (E.) Paul, D. (Salk Inst. Biol. Studies., San Diego, Calif.), A. Lipton and I. Klinger. *Proc Nat Acad Sci USA* 68(3):645-648, 1971.

Normal and SV40-transformed mouse fibroblasts were incubated with sera from rat, mouse, fetal calf, calf, human and horse to determine which of these sera promoted the growth of the fibroblasts. Mouse serum stimulated the growth of the normal cells by 210% and stimulated the growth of the transformed cells by 182%; rat serum stimulated both normal and transformed cells by 100%. Horse serum was the least effective growth promoter tested; normal cells treated with horse serum showed a 31% increase in growth while transformed cells showed a 7% increase in growth. Fractionation of rat serum by electrophoresis yielded 3 peaks; peak I (molecular weight = 50,000-70,000) promoted the growth of virus-transformed mouse cells but did not promote the growth of untransformed cells. Peak II (molecular weight = 20,000-35,000) promoted the growth of normal cells but did not promote the growth of virus-transformed cells. Peak III (molecular weight = 5,000 or above) promoted the growth of transformed, but not of untransformed, mouse cells. Rat serum also appeared to contain a fourth growth factor, one which sustained the viability of both normal and SV40-transformed cells in serum-free media without promoting cell growth.



- 0430 PRESENCE OF CELL AND VIRUS SPECIFIC SEQUENCES IN THE SAME MOLECULES OF NUCLEAR RNA FROM VIRUS TRANSFORMED CELLS. (E.) Wall, R. (Dept. Biol. Sci., Columbia U., New York, N.Y.) and J. E. Darnell. *Nature* 232(29):73-76, 1971.

The nuclear events involved in the production of polysomal mRNA in mammalian cells were investigated. Hybridization studies were carried out with 3T3, SV3T3 and BSC-1 mouse cells grown as monolayers to study the transcription of SV40 DNA in transformed cells. Hybridization conditions were used in which no molecular breakage occurred during incubation and specific hybrid formation could be achieved without the necessity of RNAase treatment. The hybridization of polysomal RNA from SV3T3 cells to SV40 DNA filters was 6 to 12 times better than to blank filters. When equivalent amounts of radioactive polysomal RNA from 3T3 cells were exposed to SV40 DNA, the amount of radioactivity bound was only slightly higher than that bound to blank filters. The selection of virus-specific RNA appeared to be both dependent on SV40 DNA on the filters and specific for RNA from transformed cells. When undegraded polysomal RNA from SV3T3 and untransformed 3T3 cells was hybridized to 20 $\gamma$  SV40 DNA filters for 8 hr in 30% formamide hybridization solution at 45°C, a substantial fraction of the SV3T3 polysomal RNA which was initially selected on SV40 DNA rehybridized to viral DNA. The viral DNA-selected polysomal mRNA from transformed cells was composed largely of SV40-specific sequences since 40% of the selected RNA hybridized back to SV40 DNA. Apparently, nuclear RNA in transformed cells contains both host- and virus-specific sequences.

- 0431 CHROMOSOMAL CHANGES IN SYRIAN HAMSTER CELLS TRANSFORMED BY SIMIAN VIRUS 40 (SV40) AND VARIANTS OF DEFECTIVE SV40 (PARA). (E.) Nachtigal, M. (Baylor Coll. Med., Houston, Texas), J. L. Melnick and J. S. Butel. *J Nat Cancer Inst* 47(1):35-45, 1971.

Chromosomal alterations were investigated in cultured hamster cells transformed by SV40 or by different variants of PARA (defective SV40)-adenovirus hybrid populations and in spontaneously transformed hamster embryo cells. SV40-transformed hamster lung cells, which did not contain SV40 tumor antigen, had a normal diploid chromosome complement and showed increased numbers of D chromosomes in 50% of diploid cells. The number of cells with chromosome breaks was relatively low (< 15%) in all SV40-transformed hamster cell lines; dicentric were found in 10-20% of these cells. Some SV40-transformed hamster cell lines showed a high percentage of double minutes. PARA-transformed hamster cell lines tended to have fewer acrocentric D group chromosomes. Early passages of lung cells transformed by 3 monoclonal variants of PARA-adenovirus 7 had lower incidences of dicentric chromosomes than companion cultures of lung cells transformed by oncogenic variants. Early passages of lung cells transformed by PARA-adenovirus 16 had the highest incidence of numerical and structural

chromosome aberrations. Hamster kidney cells transformed by oncogenic and nononcogenic variants of PARA-adenovirus 7 showed a frequency of chromosome aberrations similar to or slightly higher than that of SV40-transformed cells. Spontaneously transformed hamster embryo cells were predominantly diploid and rarely manifested chromosome aberrations.

- 0432 INFECTION AND TRANSFORMATION OF MOUSE PERITONEAL MACROPHAGES BY SIMIAN VIRUS 40. (E.) Mauer, J. (Wistar Inst., Philadelphia, Pa.) and V. Defendi. *J Exp Med* 134(2):355-350, 1971.

Peritoneal macrophages from C57BL mice were infected with SV40 (0.5-1.0 PFU/cell) and the changes in macrophages were observed. Infection of macrophages with SV40 induced DNA synthesis; as many as 70% of macrophages showed DNA synthesis by 48 hr postinfection. On the other hand, mock-infected macrophages did not synthesize DNA. Tumor antigen also appeared in SV40-infected cells. Immunofluorescence tests run on SV40-infected macrophages to detect the presence of viral antigen were consistently negative. No newly synthesized SV40 DNA could be discovered in infected cells. When the induction of DNA synthesis by SV40 infection was compared with that induced by conditioned medium, it was found that both conditioned medium and SV40 induced similar rates of DNA synthesis in macrophages until 9 days after conditioned medium treatment; at this point, DNA synthesis in cells treated with conditioned medium dropped off, while DNA synthesis in SV40-infected cells continued unpaired. SV40-transformed macrophages were established in culture; cells *in vitro* were of 2 types: large fibroblastic cells and smaller cells with cytoplasmic filaments. Cells of the former type were positive for tumor antigen, and negative for acid phosphatase and phagocytic activity, while cells of the latter type were tumor-antigen positive and showed pronounced phagocytic and acid phosphatase activity. Clones derived from cultured transformed cells showed strong fluorescence for SV40 tumor antigen. When SV40-transformed macrophages were implanted in the backs of C57BL mice pretreated with 650 R of X-irradiation, no tumor nodules developed.

- 0433 CELL SURFACE CHANGES AFTER INFECTION WITH ONCOGENIC VIRUSES: REQUIREMENT FOR SYNTHESIS OF HOST DNA. (E.) Sheppard, J. R. (Dept. Biochem. Sci., Princeton U., N.J.), A. J. Levine and M. M. Burger. *Science* 172(3990):1345-1346, 1971.

Mouse (3T3) and monkey (CV-1 and BSC) cell cultures were infected with SV40 or adenovirus 5 and the agglutinability of infected cells (associated with the exposure of the wheat germ agglutinin site on the cell surface) was observed. Agglutinability in-

creased 5-10-fold within 24-72 hr after virus infection in CV-1 cells infected with adenovirus; in BSC cells infected with SV40, agglutinability did not increase following virus infection, and in 3T3 cells infected with SV40 it increased only slightly. It was noted that DNA synthesis was not induced by SV40 infection in BSC cells, the only infected cells to show no increased agglutinability following virus infection. To determine whether inhibition of DNA synthesis would prevent exposure of the wheat germ agglutinin site on the surface of virus-infected cells, DNA synthesis in infected cells was inhibited by treating cultures with fluorodeoxyuridine. Inhibition of DNA synthesis delayed the exposure of the wheat germ agglutinin site in virus-infected cells. The findings apparently indicated that synthesis of host cell DNA is required for the observed exposure of the agglutinin site on the altered surfaces of virus-infected cells.

- 0434 ANALYSIS OF THE EVENTS LEADING TO SV40-INDUCED CHROMOSOME REPLICATION AND MITOSIS IN PRIMARY MOUSE KIDNEY CELL CULTURES. (E.) May, E. (Dept. Molec. Biol., U. Geneva, Switzerland), P. May and R. Weil. *Proc Nat Acad Sci USA* 68(6):1208-1211, 1971.

Mouse kidney cells in culture were abortively infected with SV40 virus at 37° C and the temporal relationship between the appearance of T-antigen and the onset of SV40-induced cellular DNA synthesis in infected cells was observed. T-antigen could first be detected in SV40-transformed cells 6-7 hr after infection; by 21 hr postinfection, 40-45% of cell nuclei gave positive immunofluorescence reactions for T-antigen. Autoradiographic studies indicated that at 9-10 hr postinfection the number of infected cells synthesizing DNA began to increase above levels seen in uninfected cells; by 21 hr postinfection, a maximum of 30% of the cells were synthesizing DNA. In all experiments, the increase in the number of T-antigen positive cells occurred 2-3 hr prior to the increase in the number of DNA-synthesizing cells. No evidence was found for the replication of SV40 DNA in infected cells; the SV40 capsid antigen was not detectable. It was concluded that SV40-induced cellular DNA synthesis and mitosis were confined to cells which contained SV40 T-antigen, and that most T-antigen-positive cells participated in cellular DNA synthesis.

- 0435 THE SUSCEPTIBILITY TO SV40 VIRUS TRANSFORMATION OF FIBROBLASTS OBTAINED FROM PATIENTS WITH DOWN'S SYNDROME. (E.) Young, D. (Western Gen. Hosp., Edinburgh, Scotland). *Europ J Cancer* 7:337-339, 1971.

Skin biopsy specimens were taken from the deltoid region of the arms of 4 patients with Down's syndrome and from the arms of 3 normal subjects; tissue culture lines were established from these specimens and infected with SV40 between the 5th and the 15th subculture. The cultured fibroblasts from Down's syndrome patients were more susceptible to transformation by SV40 than were

fibroblasts from healthy subjects. In normal cultures infected with SV40, numbers of transformed colonies/culture dish ranged from 3.57-4.22 over 5 separate experiments; in Down's syndrome cultures infected with SV40 the numbers of transformed colonies/culture dish ranged from 7.50-13.80.

- 0436 THE REPLICATION OF THE RING-SHAPED DNA OF POLYOMA VIRUS: II. IDENTIFICATION OF MOLECULES AT VARIOUS STAGES OF REPLICATION. (E.) Bourgaux, P. (University Hosp. Ctr., U. Sherbrooke, Quebec, Canada), D. Bourgaux-Ramoisy and P. Seiler. *J Molec Biol* 59(1):195-206, 1971.

Mouse embryo cells were infected with polyoma virus and viral DNA was selectively extracted; the replicative intermediate of the viral DNA (i.e., component II\*) was isolated using dye buoyant density-gradient centrifugation. Component II\* material was sedimented in sucrose solutions and it was found that this component sedimented more rapidly than the heavier DNA components I and II. Component II\* formed a broad band, suggesting that this portion of the viral DNA was heterogeneous. When <sup>3</sup>H-thymidine labeled component II\* was subjected to dye buoyant density-gradient centrifugation it was found that component II\* sedimented as a mixture of circular and linear single-stranded DNA of viral length. Sedimentation of component II\* at neutral and alkaline pH showed that the heterogeneous nature of II\* reflected the presence in this component of molecules which differed in molecular weight as a consequence of containing replicating DNA chains of varying lengths. When purified <sup>3</sup>H-thymidine-labeled viral DNA component II\* was examined under the electron microscope further evidence was found that this component contained molecules at different stages of replication. Replicating polyoma virus DNA of component II\* was seen to consist of circular molecules with 2 branch points, 3 branches and no free end.

- 0437 ENHANCED GLYCOLIPID:α-GALACTOSYLTRANSFERASE ACTIVITY IN CONTACT-INHIBITED HAMSTER CELLS, AND LOSS OF THIS RESPONSE IN POLYOMA TRANSFORMANTS. (E.) Kijimoto, S. (Sch. Pub. Hlth. Comm. Med., U. Washington, Seattle) and S. Hakomori. *Biochem Biophys Res Commun* 44(3):557-563, 1971.

Normal and polyoma virus-transformed hamster fibroblasts were grown in culture at different cell population densities and the activity of UDP-galactosylceramide α-galactosyltransferase in sparse cultures and in contact-inhibited cultures was observed. Enzyme activity was enhanced 2-3-fold in contact-inhibited cultures by comparison to sparse cultures. In normal hamster cell cultures with cell populations of 5 x 10<sup>4</sup> cells/cm<sup>2</sup> or less, there were 109 μmoles of glycolipid synthesized/mg protein/hr; in normal cultures in which contact inhibition of growth was in effect (i.e., cultures in which the cell population was at least 10<sup>5</sup> cells/cm<sup>2</sup>) the



synthesis of glycolipids was at 385  $\mu$ moles/mg protein/hr. The enhancement of glycolipid synthesis in high-density cell populations was abolished by infection of cultures with polyoma virus. In sparse cultures of polyoma virus-infected hamster cells the synthesis of glycolipid was 55  $\mu$ moles/mg protein/hr, while in contact-inhibited cultures the glycolipid synthesis rate was 48  $\mu$ moles/mg protein/hr. Enzymes other than UDP-gal:lactosylceramide  $\alpha$ -galactosyl-transferase were not similarly affected by contact inhibition of cell growth; UDP-gal:glucosylceramide  $\beta$ -galactosyltransferase did not increase as cell population density increased and was not affected by virus transformation of cultures.

0438 MOUSE TUMOR INDUCED BY POLYOMA VIRUS:  
I. ESTABLISHMENT OF AN EPITHELIOID CELL  
LINE SPONTANEOUSLY RELEASING POLYOMA VIRUS IN  
VITRO. (E.) Taguchi, F. (Sch. Hygienic Sci.,  
Kitasato U., Tokyo, Japan), Y. Yoshida, K. Hasegawa,  
D. Nagaki and K. Takada. *Kitasato Arch Exp Med*  
42(1-2):59-67, 1969.

Mice of the C3H/e strain developed solid s.c. adenocarcinomas following inoculation with polyoma virus; tumors were transplantable to homologous hosts. Sera from tumor-bearing mice showed hemagglutination-inhibition activity, suggesting the presence of virus in tumor cells. Cells of the polyoma virus-induced adenocarcinomas were established in culture; after 30 days these cells proliferated rapidly and showed little tendency to form clumps. Cultured tumor cells produced polyoma virus, with titers ranging from 5-80 hemagglutinating U; the hemagglutination activity of tumor cells was specifically inhibited by anti-polyoma virus immune sera derived from mice and rabbits. Tumor cells were epithelioid. C3H/e mice injected with  $10^6$  cultured tumor cells, developed s.c. adenocarcinomas within a week. Neither hemagglutinating activity nor infectious virus was detected in re-cultured cells taken from tumors induced by cultured tumor cells.

0439 RESTORATION OF CONTACT-INHIBITED GROWTH TO  
TRANSFORMED CELLS BY DIBUTYRYL ADENOSINE  
3':5'-CYCLIC MONOPHOSPHATE. (E.) Sheppard, J. R.  
(U. Colorado Med. Ctr., Denver). *Proc Nat Acad Sci*  
USA 68(6):1316-1320, 1971.

Strain 3T3 mouse cells which had transformed spontaneously or which had been transformed by polyoma virus were established in culture and the effect of dibutyryl cyclic AMP ((But)<sub>2</sub>cAMP) and theophylline on the growth of the transformed cells was observed. Spontaneous and viral transformed 3T3 cells grew rapidly in the absence of (But)<sub>2</sub>cAMP and theophylline; 4 days after initiation of cultures, spontaneously transformed cells had reached cell densities of  $22 \times 10^4$  cells/cm<sup>2</sup> and viral transformed cells had reached similar densities. Untransformed 3T3 cells, growing under conditions of contact inhibition, showed densities of  $5 \times 10^4$  cells/cm<sup>2</sup> on day 4. The addition of

(But)<sub>2</sub>cAMP and Theophylline to 3T3 spontaneous transformed cultures inhibited cell growth; spontaneous transformed cells with (But)<sub>2</sub>cAMP reached densities of  $6 \times 10^4$  cells/cm<sup>2</sup>. Addition of (But)<sub>2</sub>cAMP to viral transformed 3T3 cultures also inhibited cell growth; virus-transformed cultures treated with (But)<sub>2</sub>cAMP and theophylline showed densities of  $7 \times 10^4$  cells/cm<sup>2</sup> on day 4. When (But)<sub>2</sub>cAMP and theophylline were withdrawn from 3T3 cultures after reaching saturation density, contact inhibition of growth was abolished. Agglutinability of transformed cells by wheat germ agglutinin was decreased 5-fold in spontaneous transformed cells and 9-fold in virus-transformed cells by (But)<sub>2</sub>cAMP and theophylline treatment, but the effect was reversible and increased when the additives were removed.

0440 RAPID ASSAY OF MURINE LEUKEMIA VIRUS  
HELPER ACTIVITY FOR FRIEND SPLEEN FOCUS-  
FORMING VIRUS. (E.) Steeves, R. A. (Roswell  
Park Mem. Inst., Buffalo, N.Y.), R. J. Eckner,  
E. A. Mirand and R. L. Priore. *J Nat Cancer Inst*  
46(6):1219-1228, 1971.

0441 PERSISTENCE OF ROUS SARCOMA VIRUS IN TRANS-  
FORMED NONPERMISSIVE CELLS: RELATIONSHIP  
BETWEEN VIRUS INDUCTION BY ASSOCIATION WITH PER-  
MISSIVE CELLS AND gs ANTIGEN CONTENT OF TRANSFORMED  
CELLS. (E.) Vigier, P. (Fac. Sci., Orsay, Essone,  
France) and G. Bataillon. *Virology* 45:309-312, 1971.

0442 DIFFERENCES IN SUSCEPTIBILITY OF HUMAN  
CELLS TO MOUSE SARCOMA VIRUS. (E.)  
Klement, V. (Childrens Hosp. of Los Angeles, Cal.),  
M. H. Freedman, R. M. McAllister, W. A. Nelson-  
Rees and R. J. Huebner. *J Nat Cancer Inst* 47(1):  
65-71, 1971.

0443 PROPAGATION OF *Herpesvirus saimiri* IN  
HUMAN CELLS. (E.) Ablashi, D. V. (Viral  
Biol. Brnch., Natl. Cancer Inst., Bethesda, Md.),  
G. R. Armstrong and R. A. Manaker. *J Nat Cancer*  
*Inst* 47(1):241-243, 1971.

0444 A STRAIN OF HAMSTER EMBRYO FIBROBLASTS  
TRANSFORMED IN VITRO BY ROUS VIRUS.  
(Rus.) Martirosyan, D. M. (Armenian Acad. Sci.,  
Yerevan, U.S.S.R.) N. U. Nadzharyan. *Biull Eksp*  
*Biol Med* 71(5):95-98, 1971.

0445 THE MECHANISM OF STIMULATION OF VIRAL LEUKEMOGENESIS BY THE COMPLETE FREUND'S ADJUVANT. (Rus.) Ter-Grigorov, V. S. (P. A. Herzen Res. Inst. Oncol., Moscow, U.S.S.R.), O. Ya. Moskovkina, F. Tot, I. S. Irlin, Ye. S. Iyevleva, B. I. Shevelev and V. M. Bergol'ts. *Vop Onkol* 17(4):70-77, 1971.

0446 ADENOVIRUS-INDUCED CHROMOSOME ABERRATIONS IN HUMAN CELLS. (E.) McDougall, J. K. (Dept. Cancer Studies, U. Birmingham, Birmingham, England). *J Gen Virol* 12(1):43-51, 1971.

0447 EFFECTS OF MURINE VIRAL LEUKEMIA ON SPLEEN NUCLEOSIDE DEAMINASE: PURIFICATION AND PROPERTIES OF THE ENZYME FROM LEUKEMIC SPLEEN. (E.) Malathi, V. G. (New York U. Med Ctr., New York) and R. Silber. *Biochim Biophys Acta* 238(3):377-387, 1971.

See also:

- \* (Rev): 0308, 0312, 0315, 0316, 0318, 0327, 0330
- \* (Chem): 0379
- \* (Immun): 0448, 0450, 0451, 0455, 0456, 0458, 0465, 0466, 0474, 0476, 0478, 0479, 0485, 0490, 0491



0448 APPEARANCE OF EPSTEIN-BARR VIRUS-ASSOCIATED ANTIGENS IN INFECTED RAJI CELLS. (E.)

Gergely, L. (Karolinska Inst., Stockholm, Sweden), G. Klein and I. Ernberg. *Virology* 45(1):10-21, 1971.

Lymphoblastoid cells derived from a patient with Burkitt's lymphoma (Raji cells) were infected with Epstein-Barr virus (EBV) and the appearance of EBV-associated early and membrane antigens (EA and MA) and viral capsid antigens (VCA) was observed. The frequency of MA-positive cells was 60-90% 1 hr after infection; by 6-8 hr, the frequency of MA-positive cells was 10-20%. Both active EBV and UV-inactivated EBV produced this MA response in infected cells. Between 10-27 hr postinfection, the frequency of MA-positive cells increased again, attaining levels of 50-60%. EA-positive cells appeared at 10 hr postinfection and reached maximum levels (28-30% frequency) between 30-47 hr postinfection. A small percentage of cells were found to be both MA- and EA-positive; these cells tended to become MA-negative with time. No VCA synthesis was observed. Exposure of EBV to sera with high anti-MA antibody titers neutralized the virus, rendering it unable to produce EA.

0449 THE OCCURRENCE OF A SERUM FETAL  $\alpha_1$  PROTEIN IN DEVELOPING MICE AND MURINE HEPATOMAS AND TERATOMAS. (E.)

Kahan, B. (Grad. Dept. Biochem., Brandeis U., Waltham, Mass.) and L. Levine. *Cancer Res* 31(7):930-936, 1971.

Sera from fetal Swiss albino noninbred mice were examined by immunodiffusion with antiserum to fetal extract and found to harbor an antigen with the electrophoretic mobility of an  $\alpha_1$ -globulin and a molecular weight of 65,000-70,000. This antigen was found in mouse fetuses 10 days before birth; between the 12th day of gestation and the 20th day, the amount of  $\alpha_1$ -globulin in fetal mouse sera rose from 15-825 U of  $\alpha_1$ -globulin/mouse. After birth, the  $\alpha_1$ -globulin content of mouse sera fell sharply (500 U/mouse on the first day after birth, 200 U/mouse on the 5th day.) Concentrations of fetal antigen in adult tissue did not exceed 0.0025% of the concentrations of the antigen in newborn tissue. Fetal antigen was found in sera of female mice during gestation. High concentrations of the  $\alpha_1$ -globulin were also found in sera of mice bearing transplantable hepatomas; 4 days after tumor transplantation,  $\alpha_1$  fetal globulin in serum measured 3 U/ml serum, while 28 days after transplantation, there were 7,500 U/ml serum of fetal globulin in the sera of tumor-bearing mice. Mice with transplantable teratomas had lower fetal antigen levels than did mice with hepatomas. The  $\alpha_1$ -globulin was synthesized *in vitro* by a clonal line of testicular teratoma cells.

0450 ANTIBODY TO THE RNA-DEPENDENT DNA POLYMERASE OF MAMMALIAN C-TYPE RNA TUMOR VIRUSES. (E.)

Aaronson, S. A. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), W. P. Parks, E. M. Scolnick and G. J. Todaro. *Proc Nat Acad Sci USA* 68(5):920-924, 1971.

Hamster leukemia virus (MuLV) RNA-dependent DNA

polymerase was inhibited by exposure to serum from rats bearing transplantable Moloney murine sarcoma virus-induced tumors; serum from normal rats enhanced the activity of the DNA polymerase. While sera obtained from rats prior to implantation with Moloney virus-induced tumors did not inhibit MuLV RNA-dependent DNA polymerase, sera taken from rats 3 or more wk after inoculation of tumor cells inhibited the polymerase activity by more than 90%. To isolate the DNA polymerase inhibiting agent from tumor-bearing rat serum, serum was subjected to DEAE-cellulose column chromatography. In the DEAE columns, most of the inhibitory activity in the serum was eluted in a pattern similar to the DEAE column elution pattern of rat IgG. Gel filtration of serum on Sephadex G-200 showed a peak of inhibitory activity coinciding with the peak concentration of IgG. It was concluded that the MuLV RNA-dependent DNA polymerase inhibitor in tumor-bearing rat sera was an immunoglobulin, IgG. Partially purified MuLV DNA polymerase was very sensitive to inhibition by the IgG fraction of tumor-bearing rat serum; less than 10% of the polymerase activity remained after addition of 0.3  $\mu$ g of IgG. It was found that rabbit antiserum for MuLV RNA-dependent DNA polymerase inhibited polymerases of other mammalian C-type RNA tumor viruses including Rauscher, Moloney and Kirsten viruses. This finding suggested that RNA-dependent DNA polymerases from different mammalian tumor viruses are antigenically related.

0451 DETECTION OF MAREK'S DISEASE ANTIGEN IN FEATHER FOLLICLE EPITHELIUM OF CHICKENS VACCINATED AGAINST MAREK'S DISEASE. (E.)

Eidson, C. S. (Coll. Veterinary Med., U. Georgia, Athens), O. J. Fletcher, S. H. Kleven and D. P. Anderson. *J Nat Cancer Inst* 47(1):113-120, 1971.

Day-old chicks were given intra-abdominal injections of a turkey herpesvirus vaccine (HVT) and challenged with plasma from Marek's disease herpesvirus (MDV)-infected birds. Marek's disease developed in chicks given MDV without HVT, while chicks vaccinated with HVT did not develop Marek's disease. Gross Marek's disease lesions developed in birds given MDV only, but not in birds vaccinated with HVT. MDV could be isolated from the kidneys of 4-wk-old birds given injections of Marek's disease-infective plasma when 1-day-old. HVT isolates, as well as MDV, could be detected in kidney cells from 4-wk-old birds vaccinated with HVT following inoculation with Marek's disease-infective plasma. Sonically treated skin tissue from birds vaccinated with HVT and challenged with MDV also contained MDV. In addition to HVT isolates and MDV, vaccinated birds also harbored antibodies against these antigens. By 4 wk after inoculation with Marek's disease-infective plasma, MDV antigen was detectable in the feather follicle epithelium of unvaccinated birds; antigen was detectable in feather follicle epithelium of vaccinated birds by 6 wk after MDV challenge. Marek's disease lesions developed on 1-day-old chicks inoculated with plasma from HVT-vaccinated, MDV-infected donors; plasma donors harbored both MDV and HVT antigens.



- 0452 DEPENDENCE OF CONCOMITANT TUMOR IMMUNITY ON CONTINUED ANTIGENIC STIMULATION. (E.) Gershon, R. K. (Yale U. Sch. Med., New Haven, Conn.), K. Kondo. *J Nat Cancer Inst* 46(6):1169-1175, 1971.

Twelve hamsters were inoculated with  $1 \times 10^7$  hamster lymphoma cells; hamsters were allowed to retain the tumor inocula for 1 or 2 wk, at the end of which time tumors were excised and peritoneal exudates from tumor-bearing hamsters were tested for immunogenicity in hamsters inoculated with peritoneal exudate and tumor cells. In recipient hamsters given 1:1 mixtures of tumor cells and peritoneal exudate prepared from hamsters which had borne tumors for 2 wk before resection none of 6 recipients developed tumors following injection of the mixture. However, recipients given a 1:1 mixture prepared from hamsters which had borne tumors for 1 wk before resection developed tumors in all of 6 cases. In a related experiment, hamsters were given injections of  $5 \times 10^6$  or  $5 \times 10^7$  lymphoma cells; lymphomas were excised from half the tumor-bearing hamsters 7 days later and cell transfer tests with peritoneal exudate were performed. Peritoneal exudate from hamsters with intact tumors suppressed tumor growth in recipients regardless of the size of the original dose of lymphoma cells given to donor animals. However all of 6 hamsters receiving exudate from resected-tumor hamsters given  $5 \times 10^6$  tumor cells developed tumors and 2 of 6 hamsters receiving exudate from resected tumor hamsters given  $5 \times 10^7$  tumor cells developed tumors. The ability of hamsters bearing lymphomas to reject a tumor challenge at various intervals after resection of the original tumor was tested; it was found that resection of tumors soon after inoculation of the original tumorigenic dose of tumor cells resulted in lowered immunity to a second tumor challenge. Lowering the initial dose of tumor cells increased the period during which the hamsters were susceptible to a second tumor challenge after resection of the initial tumor. Reinoculation of  $1 \times 10^7$  tumor cells at the site of tumor resection immediately after resection of the tumor prevented the loss of transferable tumor immunity.

- 0453 SUGGESTIVE EVIDENCE THAT THE "BLOCKING ANTIBODIES" OF TUMOR-BEARING INDIVIDUALS MAY BE ANTIGEN-ANTIBODY COMPLEXES. (E.) Sjögren, H. O. (Pacific Northwest Res. Fdn., Seattle, Wash.), I. Hellström, and K. E. Hellström. *Proc Nat Acad Sci USA* 68(6):1372-1375, 1971.

Sera from mice bearing Moloney virus-induced sarcomas or 3-methylcholanthrene-induced sarcomas were mixed with cells from the 2 tumors; after 45 min of incubation, sera were withdrawn and tumor cells were exposed to lymphocytes immune to the tumor-specific antigens of the 2 tumors. The ability of sera from tumor-bearing mice to block the cytotoxic effect of immune lymphocytes was observed by measuring the decline in tumor cells following exposure to lymphocytes; a 56% effective blocking of cytotoxicity was observed. When sera from virus-induced tumor-bearing mice was absorbed with  $25-80 \times 10^6$  virus-induced tumor cells the blocking activity of serum was abolished. How-

ever, elution of sera at a low pH restored the blocking effect; a 68.2% effective blocking of lymphocyte cytotoxicity was seen for the eluted serum. The removal of the blocking effect of serum by absorption with tumor cells was specific for the virus-induced and methylcholanthrene-induced tumors; when serum from mice with methylcholanthrene-induced tumors was absorbed with cells from the virus-induced tumor the serum blocking effect was not impaired. Sera from virus- and methylcholanthrene-induced tumor-bearing mice were eluted at pH 3.1 and fractionated by ultrafiltration, yielding high (above 100,000) and low (10,000-100,000) molecular weight fractions. It was found that neither of these fractions blocked lymphocyte cytotoxicity for tumor cells when individually added to tumor cells. However treatment with both fractions blocked lymphocyte cytotoxicity. These results indicated that the blocking activity of sera from tumor-bearing mice was mediated by an antigen-antibody complex.

- 0454 INHIBITION OF PHYTOHEMAGGLUTININ-INDUCED *IN VITRO* LYMPHOCYTE TRANSFORMATION BY SERUM FROM PATIENTS WITH CARCINOMA. (E.) Sample, W. F. (Natl. Cancer Inst., Bethesda, Md.), H. R. Gertner, Jr. and P. B. Chretien. *J Natl Cancer Inst* 46(6):1291-1297, 1971.

Blood lymphocytes from normal subjects and from 120 patients with nonlymphomatous malignancies were mixed with autologous serum and treated with phytohemagglutinin (PHA); the reactivity of lymphocytes in autologous serum was determined by quantitation of PHA-induced  $^3\text{H}$ -thymidine uptake. The reactivity of normal lymphocytes correlated negatively with age of the serum donor; the maximum uptake of  $^3\text{H}$ -thymidine ( $400 \times 10^3$  dpm) was reached with subjects aged 20-yr-old or younger, whereas the minimum uptake of  $^3\text{H}$ -thymidine ( $200 \times 10^3$  dpm) was found for subjects aged 60-yr-old or older. Similar reactivity patterns in autologous sera were found for lymphocytes from cancer patients; differences in  $^3\text{H}$ -thymidine uptake by PHA-stimulated lymphocytes from normal subjects and cancer patients were not statistically significant. Reactivity patterns of lymphocytes from normal subjects and cancer patients in homologous pooled AB serum from healthy donors were also similar. In a related experiment, lymphocytes from normal subjects were mixed with sera taken from 9 cancer patients; lymphocytes from the cancer patient donors had previously been shown to have low reactivity in autologous sera. The peak PHA-induced reactivity of normal lymphocytes cultured in sera from cancer patients was significantly lower than the reactivity in homologous pooled AB serum. In normal lymphocytes cultured with pooled AB sera from normal donors the ratio of  $^3\text{H}$ -thymidine uptake in normal autologous sera to  $^3\text{H}$ -thymidine uptake in homologous pooled AB sera ranged from 0.71-1.26 (mean = 0.98). In normal lymphocytes cultured in sera from cancer patients the ratio of  $^3\text{H}$ -thymidine uptake in sera from cancer patients to  $^3\text{H}$ -thymidine uptake in homologous pooled AB sera ranged from 0.79-0.91 (mean = 0.89). The results were thought to show that an inhibitor of normal lymphocyte reactivity to PHA operates in sera of carcinoma patients.



0455 THE PRESENCE OF AVIAN LEUKOSIS VIRUS GROUP-SPECIFIC ANTIBODIES IN CHICKEN SERA. (E.)

Roth, F. K. (State U. New York Upstate Med. Ctr., Syracuse), P. Meyers and R. M. Dougherty. *Virology* 45(1):265-274, 1971.

Chickens aged 2.5, 6 and 23 wk were inoculated with subgroup A or subgroup B strains of avian leukosis virus and the production of group-specific (gs) antibodies to these viruses was investigated using the complement fixation inhibition method. The subgroup A avian leukosis virus was the RAV-1 pseudotype of Rous sarcoma virus, and the subgroup B virus was the RAV-6 pseudotype of Rous sarcoma virus. In experiments with RAV-1, chickens were given an i.v. injection of 1.0 ml of virus containing  $10^7$  infectious U/ml; low-titer gs antibodies to RAV-1 first appeared in the 2.5-wk-old birds at 5 wk after challenge and in the 6-wk-old control group at 8 wk after challenge. Birds injected with RAV-1 at 23-wk-of age did not show anti-RAV-1 gs antibody. Similarly, no gs antibodies could be detected in a group of chickens congenitally infected with RAV-1. In experiments with RAV-6 similar results were obtained; birds inoculated with virus at 2.5- and 6-wk-old showed the gs antibody in 68 and 63% of cases, resp., by 12-20 wk after inoculation, whereas birds inoculated with virus at 25-wk-old showed no gs antibody 12-20 wk after treatment. About 30% of birds inoculated at 25-wk-old showed gs antibody at 8 wk postinoculation, however. Birds congenitally infected with RAV-6 did not produce gs antibody. Titers of neutralizing (ts) and gs antibodies to RAV-1 or RAV-6 were compared in sera from 70 non-congenitally-infected chickens; there was no significant difference in antibody response to the 2 viruses. GS antibody was most common in sera of birds in which the ts antibody titer was above 1/1000; all gs-positive sera showed ts titers of more than 1/200. Fifty-six percent of sera having a high ts antibody titers were gs antibody-positive. On fractionation (Sephadex G-200 columns) of gs antibody-positive sera, it was found that gs antibody activity was located in the IgG globulin fraction.

0456 ANTIBODIES TO EARLY ANTIGENS INDUCED BY EPSTEIN-BARR VIRUS IN INFECTIOUS MONONUCLEOSIS. (E.) Henle, W. (Children's Hosp. Philadelphia, Pa.), G. Henle, J. C. Niederman, E. Klemola and K. Haltia. *J Infect Dis* 124(1):58-67, 1971.

Indirect immunofluorescence tests were used to establish the titers of antibodies to early antigens (EA) and to viral capsid antigens (VCA) of the Epstein-Barr virus in sera from 200 patients with heterophil-antibody-positive infectious mononucleosis (IM) and from 60 patients with heterophil-antibody-negative IM-like disease. In addition, antibody titers were determined for 37 individuals who did not have IM at the time of serum collection, but who developed IM later. Sera taken before the onset of IM lacked VCA and EA antibodies in all cases. In patients with heterophil-antibody-positive IM, anti-VCA titers were found to range from 1:40-1:640; 25% of these IM patients were negative for anti-EA antibodies. In 75%

of IM patients with heterophil-antibodies, anti-EA titers ranged from 1:5-1:320. Anti-VCA antibody titers appeared to rise earlier than anti-EA antibody titers. Anti-VCA antibodies also seemed to be more persistent than anti-EA antibodies: by 1-3 yr after the onset of IM, anti-EA titers had usually fallen to below 1:5 while anti-VCA titers persisted in the 1:30-1:200 range. In the heterophil-antibody-negative IM patients, 4 of 30 had anti-VCA titers of 1:160 or above; these patients were the only ones to show antibodies to EA (anti-EA titers were 1:10 or 1:20). Of 24 patients with IM apparently caused by infection with cytomegalovirus, none had anti-EA antibodies.

0457 OBSERVATIONS ON THE INCREASING MALIGNANCY OF TUMOURS ON PROLONGED GROWTH: THE INFLUENCE OF IMMUNOLOGICAL CHANGES IN THE HOST. (E.) Rees, J. A. (Dept. Surg., U. Bristol, England) and M. O. Symes. *Brit J Cancer* 25(1):121-129, 1971.

Lymph node hyperplasia, splenic hyperplasia, and time of death were examined in mice implanted with spontaneously arising mammary carcinomas; the tumors which were implanted into hosts had been allowed to grow in the mice in which they arose for increasing periods of time. The immunological competence of tumor host mice was also assessed; hosts bearing succeeding tumor passages were killed and spleen cells were injected into (A x CBA)F<sub>1</sub> hybrid mice. The graft-versus-host immune reaction to spleen cells from tumor-bearing mice was observed. In general graft-versus-host reactions in mice given spleen cells from tumor-bearing mice were not impaired; it was therefore concluded that the immunocompetence of tumor-bearing mice was not reduced. The increasing malignancy of tumors of prolonged growth was thus not due to host immunodepression. Increased malignancy of tumors implanted into host mice after relatively long periods of growth in their original hosts was evidenced by a decrease in hyperplasia in ipsilateral and contralateral lymph nodes in hosts following implantation of tumors of succeeding passages. A rise in ipsilateral and contralateral lymph node hyperplasia was seen in mice implanted with tumors of passage 1 or 2; however, ipsilateral lymph node hyperplasia declined in mice given implants of passage 7 tumor and contralateral lymph node hyperplasia declined in mice given implants of passage 9 and 10 tumors. In mice given implants of passage 5-10 tumors, splenic hyperplasia increased. The killing time (i.e., elapsed time between tumor implantation and host death) of passage 1 and 2 tumors (46-47 days) was longer than that of passage 3-4 tumors (31-33 days). The results show that on serial subcutaneous passage of A-strain mouse mammary carcinomas in the strain of origin, the killing time of the tumor decreases. It is suggested that the fundamental change involved in the increasing malignancy of the tumor is a change in the tumor cells rather than increasing immunodepression in successive hosts.

0458 QUANTITATIVE *IN VITRO* MEASUREMENT OF SIMIAN VIRUS 40 TUMOR-SPECIFIC ANTIGENS. (E.)

Wright, P. W. (Nat'l. Cancer Inst., Bethesda, Md.) and L. W. Law. *Proc Nat Acad Sci USA* 68(5):973-976, 1971.

SV40-transformed and polyoma virus-transformed AL/N mouse cells were labeled with  $^{51}\text{Cr}$  and incubated with sera from AL/N mice immunized with syngeneic SV40-transformed cells or with sera from nonimmune AL/N mice; sera from allogeneic mice were also tested against  $^{51}\text{Cr}$ -labeled virus-transformed AL/N cells. Rabbit serum was added to the transformed cells and sera as a complement. The  $^{51}\text{Cr}$ -labeled SV40-transformed target cells were selectively killed in the presence of specific antibody and rabbit complement. Cytotoxicity for labeled transformed cells shown by various sera was measured as the percentage of cells lysed at a given serum dilution. In the presence of rabbit complement, SV40 immune AL/N serum, nonimmune AL/N serum and allogeneic serum were about equally cytotoxic for  $^{51}\text{Cr}$ -labeled, SV40-transformed cells; at a reciprocal serum dilution of 10 all 3 sera lysed about 100% of cells. Without the rabbit complement, none of the sera lysed more than 20% of cells. It was found that the reaction of the anti-SV40-transformed AL/N cell serum was specific for SV40-transformed cell lines. The cytotoxicity assay using  $^{51}\text{Cr}$ -labeled virus-transformed cells allowed quantitation of SV40 tumor specific transplantation antigen concentrations in transformed cells; the assay was thought to be more efficient than other assays of SV40 tumor specific antigens.

0459 FAILURE OF LONG-TERM IMMUNOLOGIC CONTROL OF 3-METHYLCHOLANTHRENE-INDUCED SKIN TUMORS IN THE AUTOCHTHONOUS HOST. (E.) Lappe, M. A. (Dept. Zool., U. California, Berkeley). *J Reticuloendothel Soc* 10(1):120-130, 1971.

Papillomas were induced in female BALB/c mice by topical application of 3-methylcholanthrene (MCA); the immunocompetence of treated mice had been altered either by treatment with bacillus Calmette-Guerin (MER), which enhanced immunity to allografts, or by treatment with anti-lymphocyte serum (ALS), which depressed immunity to allografts. Immunologic competence in mice was monitored by giving mice skin grafts from a DBA/Crgl mouse. Papillomas developed in all MCA-treated mice; the latent period for papilloma development was longer for MER-treated mice than for ALS-treated mice or for mice given no immunocompetence-modifying treatment. On day 30 after MCA-treatment, when differences among the 3 groups of mice were greatest, 41 MER-treated mice had developed 8 papillomas, 30 untreated mice had developed 12 tumors and 41 ALS-treated mice had developed 21 tumors. The mean survival time of allografts in treated mice was determined to assess the immunocompetence of mice in each of the 3 groups. The mean survival times of allografts in MER-treated, untreated, and ALS-treated mice were 15.2 days, 16 days and 20 days, resp. By 3 mo. after MCA treatment there was no significant difference between tumor incidence in the 3 groups of mice.

0460 *IN VITRO* DETECTION OF CYTOTOXIC CELLULAR IMMUNITY AGAINST TUMOR-SPECIFIC ANTIGENS BY A RADIOISOTOPIC TECHNIQUE. (E.) Jagarlamoody,

S. M. (U. Minnesota Med. Sch., Minneapolis), J. C. Aust, R. H. Tew and C. F. McKhann. *Proc Nat Acad Sci USA* 68(6):1346-1350, 1971.

$^3\text{H}$ -Thymidine-labeled cells from BALB/c mouse tumors and human tumors were used to evaluate the cytotoxic cellular immune response against tumor-specific antigens; the cytotoxicity of immune lymphocytes was measured by observing the loss of labeled target cells from the surface of the culture vessel. Mouse rhabdomyosarcomas were induced by Moloney sarcoma virus; immune lymphocytes were prepared from spleens of mice bearing regressed tumors. Incubation of tumor cells with spleen cells from immune mice reduced the target tumor cell population by 49-79%, while incubation of rhabdomyosarcoma cells with tumor-free mice gave a 4-23% reduction of target cells. Immune spleen cells from mice with virus-induced rhabdomyosarcomas were not cytotoxic to tumors induced in mice by 3-methylcholanthrene. In experiments with human tumor cells target tumor cells included cells from malignant melanoma, neuroblastoma, rhabdomyosarcoma, adenocarcinoma of the ovary and glioblastoma. Lymphocytes were taken from the blood of tumor-bearing patients; lymphocytes from all patients except the glioblastoma patient reduced cell populations of autologous tumor cells (37-43% reductions). Lymphocytes from tumor-bearing patients were also cytotoxic to cells from histopathologically similar tumors from different hosts (13-70% reductions of target cell populations). Lymphocytes from tumor-bearing patients failed to destroy either histologically dissimilar tumor cells or autologous non-tumor cells. In related experiments, tumor cells from tumor-bearing patients were treated with serum from the same patients prior to incubation of tumor cells with autologous lymphocytes; in all cases, the cytotoxicity for tumor cells of autologous lymphocytes was blocked by treatment with autologous serum.

0461 THE IDENTIFICATION OF A THERMORESISTENT ANTIGEN IN NORMAL AND LEUKEMIC HUMAN TISSUES.

(Rus.) Chechik, B. E. (P. A. Herzen Res. Inst. Oncol., Moscow, U.S.S.R.), V. F. Shekolookin, F. L. Kiselev. *Biull Eksp Biol Med* 71(5):89-92, 1971.

A thermoresistent corpuscular cross-reacting antigen, referred to as the Y antigen, isolated from human leukemic spleen tissue was characterized. Its preliminary purification was carried out by ultracentrifugation in a 20-60% sucrose gradient, whereby 90% of the Y antigen activity appeared to be concentrated within a yellow layer. This layer was subjected to further centrifugation in a CsCl gradient. Electron microscopy of the 1.58 g/ml density layer revealed the presence of 100-115 Å size particles which were similar to ferritin; no ribosomes or fragments of ribosomes were found in this fraction. Further investigation confirmed the Y antigen to be constituted of ferritin; this ferritin appeared to be similar to ferritin from monkey, cow and mouse tissue. The occurrence of increased amounts of Y antigen in leukemic patient tissue may be attributed to enhanced



decay processes of defective erythrocytes leading to increased iron levels which induce the synthesis of apoferritin.

- 0462 HERPESVIRUS ANTIBODY AND CARCINOMA *IN SITU* OF THE CERVIX. (E.) Catalano, L. W., Jr. (Natl. Inst. Child Hlth. Human Devel., Natl. Inst. Hlth., Bethesda, Md.) and L. D. Johnson. *JAMA* 217 (4):447-450, 1971.

A serologic study was performed for the presence of type-specific *Herpesvirus hominis* antibodies in women; studies were made at 3 periods of time: prior to development of carcinoma *in situ*, during the stage of carcinoma *in situ*, and after treatment for carcinoma *in situ* by cervical conization. Patients and controls were similar in age, income, gravidity, race, age at time of marriage and number of years married (it was noted, however, that there were no Negroes in the pre-carcinoma *in situ* group, in contrast to the other 2 groups). Five of 14 women who developed carcinoma *in situ* 1-8 years after testing had type 2 antibody responses to *Herpesvirus hominis* whereas type 2 antibodies were present in 2 of 28 controls who did not develop carcinoma *in situ* during the same period of observation. Thirteen of 31 women with carcinoma *in situ* had type 2 viral antibodies while 11 of 62 controls without carcinoma *in situ* had antibodies. One of 11 women who had been successfully treated for carcinoma *in situ* had type 2 virus antibodies while 7 of 22 controls (women without carcinoma *in situ* who had not had cervical conization) had antibodies. The data suggests that previous herpesvirus type 2 infection is associated not only with the precursory stages of invasive cancer, but also precedes the earliest intraepithelial changes which develop into carcinoma *in situ*.

- 0463 TUMOUR GROWTH IN RELATION TO THE IMMUNOLOGICAL ENVIRONMENT. (E.) Riches, A. C. (Med. Sch., Birmingham, England) and D. B. Thomas. *Advances Exp Med* 15:361-372, 1971.

The growth of tumor implants in syngeneic and allogeneic mouse recipients, as it is affected by modifications in the immunocompetence of recipients, was investigated; mice of the CBA and CS1 strains were used, and the tumor implanted was a murine mammary adenocarcinoma. Tumor implants grew well in syngeneic recipients (CBA), increasing in size 5-fold between days 4-14 after implantation; in allogeneic recipients (CS1) the tumor was rejected within 16 days after implantation. CBA mice which had received an initial syngeneic tumor implant accepted a second implant readily; however, CS1 mice which had rejected an initial allogeneic implant rejected a second implant within 12 days after implantation. Tumor implants grew well in allogeneic recipients exposed to 600 R of whole-body X-irradiation; implants increased 5-fold in size between days 4-14 after implantation. In allogeneic recipients, exposed to 300 R of radiation the tumor implants grew

more slowly; in mice given 300 R, implants increased 2.5-fold in size between days 4-14 after implantation. Administration of antilymphocyte serum (ALS) to allogeneic tumor recipients resulted in rapid growth of tumor implants. Whereas recipients which had initially rejected a tumor allograft continued to reject subsequent allografts despite exposure to X-irradiation, recipients treated with ALS accepted both initial and subsequent allografts. When mice were exposed to lethal doses of X-irradiation (820 R) and injected with spleen cells prior to implantation of a tumor allograft it was found that the capacity for rejection of the allograft in irradiated mice recovered within 1 month except in cases in which allograft challenge occurred immediately after injection of spleen cells. Bone marrow cells also protected recipients against tumor allografts. Irradiated mice treated with spleen cells from donors which had previously rejected an initial allograft were able to reject tumor implants immediately after injection of spleen cells.

- 0464 CHARACTERIZATION OF IMMUNOGLOBULIN STRUCTURES FROM THE SURFACE OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS. (E.) Eskeland, T. (Anat. Inst., U. Oslo, Norway), E. Klein, M. Inoue and B. Johansson. *J Exp Med* 134(1):265-280, 1971.

Leukemic blood cells with large amounts of  $\mu$  and  $\kappa$  immunoglobulin structures on the cell surface and relatively small amounts of intracellular  $\mu$  and  $\kappa$  structures were taken from a male patient with chronic lymphocytic leukemia and homogenized prior to centrifugation at 2000 g. The supernatant contained  $\mu$  and  $\kappa$  structures, as demonstrated either by its inhibition of passive hemagglutination or by fluorescence staining. The amounts of  $\mu$  and  $\kappa$  structures sedimented by centrifugation increased as the speed of centrifugation increased. However, centrifugation of light-centrifuge supernatants at 80,000 g for 30 min left  $\mu$  and  $\kappa$  structures in the supernatant. Ultracentrifugation at 105,000 g also left  $\mu$  and  $\kappa$  structures in the supernatant. Immunoglobulin-containing supernatants were mixed with rabbit 7S  $\gamma$ -globulin and subjected to density gradient centrifugation in order to determine the size of the  $\mu$  and  $\kappa$  structures. The  $\mu$  and some of the  $\kappa$  structures were found to sediment on density gradient centrifugation in a similar manner to 7S rabbit  $\gamma$ -globulin. Other  $\kappa$  structures were apparently of a smaller size. Evidently, the  $\mu$  and some of the  $\kappa$  structures were chains forming 7S IgM molecules, while some of the  $\kappa$  structures occurred as free  $\kappa$  chains.

- 0465 SPECIES-SPECIFIC AND INTERSPECIFIC ANTIGENIC DETERMINANTS ASSOCIATED WITH THE STRUCTURAL PROTEIN OF FELINE C-TYPE VIRUS. (E.) Oroszlan, S. (Flow Labs., Inc., Rockville, Md.), R. J. Huebner and R. V. Gilden. *Proc Nat Acad Sci USA* 68(5):901-904, 1971.

A major group-specific (gs) protein of the C-type feline leukemia virus was isolated by isoelectric focusing and species-specific and interspecific anti-

genic determinants associated with the protein were discovered. Purified feline virus was labeled with  $^3\text{H}$ -amino acids and disrupted with Tween ether prior to electrofocusing; a major radioactive zone with a peak at pH 8.3 was consistently obtained which evidently contained the viral protein. The pH fraction derived from isoelectric focusing was electrophoresed on SDS-acrylamide gels; electrophoresis indicated that the molecular weight of the protein fraction was 25,000. Immunological analysis of the feline virus protein was carried out in complement fixation tests employing murine leukemia virus gs antigens, hamster leukemia virus gs antigens and feline leukemia virus gs antigens. It was found that anti-feline virus gs antiserum was specific for feline virus, anti-hamster antiserum was specific for hamster virus, and anti-mouse serum was specific for murine virus. The feline virus protein was also found to contain interspecific cross-reactive antigenic determinants.

- 0466 HOST CELL MACROMOLECULAR SYNTHESIS IN CELLS CONTAINING EBV-INDUCED EARLY ANTIGENS, STUDIED BY COMBINED IMMUNOFLUORESCENCE AND RADIOAUTOGRAPHY. (E.) Gergely, L. (Karolinska Inst., Stockholm, Sweden), G. Klein and I. Ernberg. *Virology* 45(1):22-29, 1971.

DNA, RNA and protein synthesis were observed in Raji cells infected by Epstein-Barr virus; cells containing the intranuclear early antigen induced by Epstein-Barr virus, and cells containing membrane antigen, showed different patterns of macromolecular synthesis than virus-infected cells lacking one or both of these antigens. Infected cells lacking both antigens synthesized DNA more actively than antigen-positive cells; 48 hr after virus infection the percentage of antigen-negative cells incorporating  $^3\text{H}$ -thymidine was 55% while the percentage of membrane antigen-positive and early antigen-negative cells incorporating  $^3\text{H}$ -thymidine was 25% and the percentage of early antigen-positive cells incorporating  $^3\text{H}$ -thymidine was 3%. Antigen-negative and membrane antigen-positive cells synthesized RNA at similar rates; early antigen-positive cells synthesized RNA at a rate which was 50% that of RNA synthesis in antigen-negative and membrane antigen-positive cells. Protein synthesis was inhibited in early antigen-positive cells; however there was no detectable difference between protein synthesis levels in antigen-negative and membrane antigen-positive, early antigen-negative cells.

- 0467 COMPLEMENT-FIXING ANTIGENS IN BURKITT LYMPHOMA CELL LINES. (E.) McCormick, K. J. (Baylor Coll. Med., Houston, Texas), W. A. Stenback, D. M. Mumford and J. J. Trentin. *Infect Immun* 4(1):20-22, 1971.

Cultures of 5 different lines of Burkitt's lymphoma cells were reacted with sera from healthy American donors to determine the complement-fixing (CF) activity of antigens from the lymphoma cells. Three of the 5 Burkitt's lymphoma cell lines contained Epstein-Barr virus as demonstrated by electron

microscopy. About 79% of normal sera fixed complement in the presence of antigens from the virus-positive lymphoma cells; CF antigens were not found in lymphoma cells which did not contain virus. Geometric mean titers of CF antigen in virus-positive cell cultures ranged from 4.2-5.0 ( $\log_2$  titers).

- 0468 ANTIGENS OF NASOPHARYNGEAL CARCINOMA. (E.) Nelson, D. S. (WHO Immunol. Res. Training Ctr., U. Singapore). *Clin Exp Immun* 8(6):863-869, 1971.

Sera taken from Chinese patients with nasopharyngeal carcinoma were tested against sections taken from autologous tumor biopsies using the indirect immunofluorescence test. Of 28 serum samples, 9 reacted "strongly" with tumor cell membranes, 4 reacted strongly with tumor cell nuclei and 2 reacted strongly with tumor cell cytoplasm. The incidence of serum antibodies to tumor cell membranes and/or nuclei did not rise following therapeutic irradiation of patient donors. Some sera which reacted strongly against tumor cell constituents were tested against sections of tumors from patients whose sera were unreactive and against sections of nasopharyngeal biopsies from patients without nasopharyngeal carcinoma. Of 4 sera with antibodies to tumor cell nuclei, 1 reacted with tumor cell nuclei, lymphoid cell nuclei and normal epithelial cell nuclei. All tumor cells, as well as normal epithelial cells, contained the cytoplasmic antigen.

- 0469 NEONATAL THYMECTOMY AND NON-VIRAL TUMORS IN MICE. (E.) Burstein, N.A. (Natl. Cancer Inst., Bethesda, Md.) and L. W. Law. *Nature* 231(5303):450-452, 1971.

The influence of early thymectomy on the frequency of several types of spontaneous neoplasms has been examined in 2 groups of mice, C57BL/KaLw strain mice and an F<sub>1</sub> hybrid. Both groups of mice were thymectomized at 3 days of age. All mice which presented neoplasms or died were necropsied and tissues were taken for histologic study. No significant differences were found in age at death between thymectomized and intact mice (which died from non-neoplastic causes) nor were any differences noted in body weights taken periodically through 15 months of age. A slight reduction in total peripheral leukocytes was observed at all ages studied through 18 months, as was lymphocyte depletion to 30-50% of normal levels. Hemolysin titers of sheep red blood cells were significantly lower in thymectomized mice aged 9-20 months. Both intact and thymectomized mice immunized with human serum albumin (HSA) and skin tested i.d., developed edema and erythema after 3 hr followed by induration after 24 hr. Thymectomy increased the frequency of late-occurring mammary tumors to 40% from a frequency of 4% in intact female BC3HF<sub>1</sub> mice. These tumors appeared as early as 20 months and as late as 33 months and ranged histologically from well-differentiated papillary adenocarcinomas to anaplastic carcino-



mas that infiltrated into a fibrous stroma. Neither the frequency nor the latent period of hepatomas and reticulum cell sarcomas of BC3HF<sub>1</sub> and C57BL mice was affected by early thymectomy.

- 0470 DEMONSTRATION OF AN ANTIGEN COMMON TO SEVERAL VARIETIES OF NEOPLASIA: ASSAY USING ZIRCONYL PHOSPHATE GEL. (E.) Gerfo, F. L. Columbia U. Coll. Physicians and Surgeons, New York, N.Y.), J. Krupcey and H. J. Hansen. *New Eng J Med* 285(3):138-141, 1971.

Sera or plasma from a total of 674 hospital patients was treated with perchloric acid, centrifuged and incubated with radioactive-iodine-labeled carcino-embryonic antigen (CEA) in zirconyl phosphate gel; CEA levels in the patients were determined. The normal range of CEA was known to be 2.5 ng/ml of blood. Markedly elevated levels of CEA (e.g., 21-300 ng/ml) were found in patients with hepatoma, colonic carcinoma, mammary carcinoma, lung carcinoma, gallbladder carcinoma, pancreatic carcinoma and prostatic carcinoma. Of 299 patients without apparent neoplasia, 11 had detectable serum CEA; of these 11, 1 developed hepatoma and 1 developed lung carcinoma. Elevated CEA values were most often found in patients with advanced carcinoma; in patients in the early stages of cancer, CEA values were usually near normal.

- 0471 HOST RESPONSE TO CHALLENGE WITH SA7-INDUCED AUTOCHTHONOUS TUMOR CELLS. (E.) Lausch, R. N. (Hershey Med. Ctr., Pennsylvania State U., Hershey), M. A. Jerkofsky, D. Haughton and R. Cody. *Int J Cancer* 8:10-21, 1971.

Preparations of simian adenovirus 7 (SA7) were exposed to UV irradiation and injected s.c. into less-than-1-day-old hamsters; when tumors developed they were resected. Tumor cells were either re-inoculated into the hamsters on which they had originally developed (autochthonous hosts) or inoculated into syngeneic hamsters. It was found that exposure of oncogenic SA7 to UV did not reduce the oncogenic potential of the virus, although hamsters given unexposed SA7 tended to develop tumors at a slightly faster rate than hamsters given UV-exposed SA7, and females given untreated SA7 tended to develop tumors earlier than males given unexposed virus. In 3 cases, SA7-induced tumor cells grew equally well in autochthonous hosts and in syngeneic recipients of tumor transplants. In 2 cases this finding might have resulted from the large size of the tumor cell inoculum; large numbers of challenge tumor cells might have overcome host resistance. In 9 cases, SA7-induced tumors grew in neither autochthonous hosts nor syngeneic recipients and in 12 cases tumors failed to grow in autochthonous hosts, apparently as a result of autochthonous host resistance. There were 6 cases in which tumors grew in autochthonous hosts given tumor cell inocula where the same inocula failed to produce growing tumors in syngeneic recipients. It was found that tumor cell inocula, which yielded tumors in only 3 of 14 adult hamsters, produced growing tumors in 11 of 11 infant hamsters.

- 0472 STUDIES ON THE RELATIONSHIP BETWEEN THYMUS REGENERATION AND LYMPHOMA PREVENTION IN C57BL/6 MICE IRRADIATED AND INJECTED WITH SYNGENEIC SPLEEN CELLS. (E.) Chen, L. (Weizmann Inst. SCI., Rehovoth, Israel). *Int J Cancer* 7(3):491-498, 1971.

Mice of strains C57BL/6 and DBA/2 were exposed to 170 or 200 R whole-body X-irradiation and subsequently injected with syngeneic spleen or bone marrow cells. The incidence of radiogenic lymphomas developing in mice given radiation but neither spleen cells nor bone marrow cells was 50%; the incidence of lymphomas in mice given radiation and spleen cells was 17% or 12% (depending on the number of spleen cells injected) and the incidence of lymphomas in mice given radiation and bone marrow cells was 10%. Radiation reduced the thymus weight to 19 mg; treatment of irradiated mice with spleen cells from adult mice did not bring about a regenerative increase in thymus weight, whereas spleen cells from newborn mice increased the thymus weight in irradiated mice to 42 mg. Injection of bone marrow cells increased the thymus weight in irradiated mice to 68 mg. Experiments designed to test the uptake of tritiated thymidine and <sup>14</sup>C-phenyl alanine by thymus cells of irradiated mice injected with spleen or bone marrow cells confirmed the finding that spleen cells did not promote regeneration of the damaged thymus, while bone marrow cells did promote regeneration.

- 0473 ANOMALOUS SERUM PROTEIN IN HEPATOCARCINOMA AND HEPATIC METASTASES. (E.) Lippi, U. ("P. Cosma" Hosp., U. Padua, Italy), A. Villa, R. Pavan and G. Guidi. *Amer J Clin Path* 56(2):227-229, 1971.

Serum specimens from 381 human subjects were subjected to disk electrophoresis; sera were taken from normal adults, newborns, patients with viral hepatitis, patients with hepatocarcinoma, and patients with other malignant diseases. In electrophoresis, sera from patients with hepatocarcinoma showed an extranumerical band migrating in the polyacrylamide gels as a post-albumin. The anomalous protein band was seen in 100% of patients with liver cell carcinoma with cirrhosis, in 90% of patients with liver metastases, and in 69% of a group of patients described as having "hepatocarcinoma". The anomalous protein band was seen only in patients with primary or metastatic liver carcinoma; it appeared not to have antigenic properties.

- 0474 CELL-MEDIATED AND HUMORAL IMMUNE RESPONSES TO TUMOR-ASSOCIATED AND VIRAL ANTIGENS IN RELATION TO THE PATHOGENIC EFFECT OF ROUS SARCOMA VIRUS IN RATS. (E.) Jonsson, N. (Inst. Path., U. Lund, Sweden). *Int J Cancer* 7(3):547-556, 1971.

Newborn rats were given s.c. injections of 0.1 or 0.2 ml of a suspension of Schmidt-Ruppin Rous sarcoma virus and the lymph-node cell (LNC)-mediated immunity and humoral immunity to tumor-associated transplantation antigens were investigated in tumor-bearing rats by the colony inhibition technique. Forty-seven per-

cent of virus-inoculated rats developed sarcomas over 6 months postinoculation; about half the tumor-bearing rats also developed hemorrhagic cysts. Eighteen percent of inoculated rats developed cysts but no tumors. Colony inhibition tests were performed on lymph node cells and on sera of 88 rats. LNC-mediated tumor-specific immunity was detected in 83% of tumor-bearing rats and in 93% of tumor-free rats. LNC-mediated immunity was detected in 56% of rats with cystic lesions but without sarcomas. Humoral cytotoxic immune activity was present in 80% of rats with cysts and in 55% of rats without cysts. Among tumor-bearing rats, humoral immunity was present in a slightly higher percentage of animals with cysts than in animals without cysts. Deficiency of the LNC-mediated immune response to tumor-associated transplantation antigen was apparently not related to tumor induction by the virus.

0475 LOSS OF A NORMAL COLONIC MEMBRANE ANTIGEN IN HUMAN CANCERS OF THE COLON. (E.)

Burtin, P. (Inst. Sci. Res. Cancer, Villejuif, France), S. von Kleist and M.-C. Sabine. *Cancer Res* 31(7):1038-1041, 1971.

Tissue samples taken from specimens of human colonic adenocarcinomas and colonic polyps were tested for the presence of the colonic membrane antigen detectable in normal colonic tissue. In colonic adenocarcinomas, fluorescence associated with an antigenic reaction in the cytoplasm of colonic mucosa cells was diminished compared to normal colonic mucosa, and fluorescence associated with an antigenic reaction in the plasma membranes of mucosa cells was lacking entirely. The membrane-associated antigen was markedly decreased in colonic polyps. It was noted that carcinoembryonic antigen often appeared in areas of the cancerous or precancerous colon from which the membrane-associated colonic antigen had disappeared.

0476 OCCURRENCE OF ANTIBODIES TO THE T ANTIGEN OF CHICKEN EMBRYO LETHAL ORPHAN VIRUS.

(E.) McCormick, K. J. (Baylor Coll. Med., Houston, Texas), J. P. Anderson, W. A. Stenback and J. J. Trentin. *Cancer Res* 31(7):981-984, 1971.

Newborn hamsters were inoculated i.p. or s.c. with 0.1 or 0.2 ml of prepared chick embryo lethal orphan virus (CELO); fibrosarcomas, hepatocellular carcinomas, adenocarcinomas of the liver and liver sarcomas developed. Tumor-bearing animals were killed and their sera and ascitic tumor fluids were tested for the presence of viral and tumor (T) antibodies to CELO; complement fixation and indirect immunofluorescence tests were performed. In the complement fixation test, antibodies to CELO were found in the sera of 3 of 37 fibrosarcoma-bearing hamsters and in sera and/or ascitic fluids of 2 of 3 hamsters with liver adenocarcinoma. Twenty-nine of 47 tumor-bearing hamsters produced T antibodies to CELO antigens detectable by indirect immunofluorescence. Tumors were transplanted to other hamsters in some cases; hamsters bearing transplanted tumors did not

produce CELO antibodies detectable by complement fixation. Eleven percent of hamsters bearing transplanted fibrosarcomas produced CELO antibodies detectable by immunofluorescence.

0477 BLOOD-GROUP ISOANTIGENS IN LEUKEMIC CELLS: REVERSIBILITY OF ISOANTIGENIC CHANGES BY NEURAMINIDASE. (E.) Kassulke, J. T. (U. Minnesota Med. Sch., Minneapolis), O. Stutman and E. J. Yunis. *J Nat Cancer Inst* 46(6):1201-1208, 1971.

The presence of A, B, H, M and N isoantigens was investigated in leukocytes from normal and leukemic individuals of A and B blood types; mixed agglutination and specific antibody absorption tests were employed. A, B and H antigens were detected on leukocytes from normal type A and B subjects. Leukocytes from 5 of 8 type A leukemia patients did not manifest the A antigen, and the anti-A reaction was decreased in strength in 4 other leukemia patients. The B antigen reaction was found in near-normal strengths in 5 type B leukemia patients. The anti-H mixed agglutination reaction of type A and type B leukemic patients was decreased in strength in 8 of 15 tests. M and N antigens, which were not detectable in normal subjects, were found in some leukemic patients. When leukocytes from normal and leukemic subjects were treated with neuraminidase, it was found that neuraminidase did not affect the amount of A, B or H antigens on normal leukocytes; neuraminidase also failed to affect the inability to detect M or N antigens on normal leukocytes. Neuraminidase, however, increased the amount of A and H antigens on leukemic leukocytes; whereas untreated leukemic leukocytes showed less H antigen than normal leukocytes, 4 of 8 samples of neuraminidase-treated leukemic leukocytes showed amounts of H antigen comparable to those seen in normal leukocytes. In 4 of 5 cases, treatment increased the amount of A antigen on leukemic leukocytes to values comparable to those seen on normal leukocytes. Neuraminidase treatment of leukemic leukocytes decreased the amounts of M and N antigens detectable on those leukocytes. Neuraminidase treatment did not significantly affect the amount of B antigen detectable on leukemic leukocytes.

0478 IMMUNOSUPPRESSION DURING LEUKEMOGENESIS: NATURE AND MECHANISM. (E.) Ceglowski, W. S. (Coll. Sci., Pennsylvania State U., University Park). *Ann NY Acad Sci* 181:272-278, 1971.

In a review of recent experiments, the finding that infection with murine leukemia virus can lead to loss of immunocompetence in the infected animals was discussed. Studies using Friend, Gross, Moloney and Rauscher murine leukemia viruses have shown that the immune response of animals infected with these agents to such antigens as sheep red blood cells, T<sub>2</sub> bacteriophage, bovine serum albumin, influenza virus and passive hemagglutinins is consistently impaired. In one study, reduced antibody titers to antigen in Friend virus-infected mice were found when mice were infected with virus prior to antigenic challenge, but



not when mice were infected after challenge. Murine leukemia viruses apparently affect both cellular and humoral immunity in their hosts. Results of studies of the effect of murine leukemia virus infection on the secondary immune response in infected hosts are conflicting; some experiments indicate that infected animals have an impaired secondary immune response while other experiments indicate that viral infection does not affect the secondary immune response. There is some evidence that leukemia viruses do not inhibit the formation of antibodies in committed antibody-forming cells. Although thymic cells from virus-infected animals have been shown to reconstitute successfully the immune response of irradiated syngeneic animals, bone marrow cells from infected donors cannot restore the immune response in recipients. The precise mechanism by which murine leukemia viruses suppress the immune response is not clear.

- 0479 DEMONSTRATION AND IDENTIFICATION OF CYTOTOXIC ANTIBODIES AND ANTIBODIES BLOCKING THE CELL-MEDIATED ANTITUMOR IMMUNITY AGAINST ADENOVIRUS TYPE 12-INDUCED TUMORS. (E.) Ankerst, J. (Dept. Med. Microbiol., U. Lund, Sweden). *Cancer Res* 31(7):997-1003, 1971.

Adenovirus-induced rat tumor cells were labeled with  $^{51}\text{Cr}$  and exposed to sera from mice immunized against the tumor-specific transplantation antigen. Using the  $^{51}\text{Cr}$  release technique it was established that sera from syngeneic adenovirus tumor-immunized mice were cytotoxic for adenovirus-induced rat tumor cells in the presence of human or sheep serum complement. Sera from mice immunized with tumors induced by Rous or polyoma virus failed to express this specific cytotoxicity. Lymph node cells from mice immunized with adenovirus-induced tumor cells inhibited colony formation of adenovirus-induced rat tumor cells. However, sera from mice immunized with adenovirus-induced tumor cells blocked this colony-inhibiting effect of lymph node cells from immunized mice. Antisera from mice immunized against the adenovirus-induced tumor were chromatographically fractionated on Sephadex G-200; after the elimination of the 19S fraction, antisera were separated on DEAE ion-exchange cellulose to obtain 19S and 7S  $\gamma$ -globulins in a pure form. The cytotoxic activity of the 19S and 7S antiserum fractions was compared with that of unfractionated serum and of serum from unimmunized mice. Unfractionated antisera and 19S antiserum fractions were clearly cytotoxic for adenovirus-induced rat tumor cells when compared with sera from nonimmunized mice. The 7S antiserum fraction showed no complement-fixing cytotoxic activity. Unfractionated sera and the 7S antiserum fraction protected rat adenovirus-induced tumor cells against the colony-inhibiting effects of immune mouse lymph node cells; neither serum from unimmunized mice nor the 19S antiserum fraction showed such protective activity.

- 0480 IMMUNOLOGICAL STUDIES IN HODGKIN'S DISEASE. (Fr.) Amiel, Y. L. (Gustave-Roussy Inst., Villejuif, France) and M. Schneider. *Bull Cancer (Paris)* 58(1):9-20, 1971.

A parallelism is drawn between the HL-A membrane

antigen system and the mouse H-2 system, and an attempt is made to relate certain factors in Hodgkin's disease to these systems. Preliminary studies of this disease have shown that antigen 4c of the HL-A antigen membrane was found more frequently in patients with Hodgkin's disease (51%) than in normal subjects (27%). BCG responses revealed that patients in remission showed more positive reactions than those in the visible phase of the disease; transformation of lymphocytes *in vitro* showed a constant diminishing reactivity, circulating lymphocytes also showed a constant decrease; hyperchromatic basophile cells were markedly increased in the patients (this, however, was not unique to Hodgkin's disease as compared to other neoplasms); no significant differences in gamma globulins were found between patients and controls. No significant differences in lymphocyte transformation rate or in BCG reactivity were found between Hodgkin's disease patients given treatment and untreated patients.

- 0481 *IN VITRO* ACTIVATION OF LYMPHOCYTES FROM PATIENTS WITH MALIGNANT DISEASES: KINETICS AND DIFFERENCES IN MAGNITUDE OF RESPONSE. (E.) Benezra, D. (Hadassah U. Hosp., Jerusalem, Israel) and A. Hochman. *Israel J Med Sci* 7(4):553-560, 1971.

The magnitude and kinetics of the response of lymphocytes in cancer patients to stimulation with phytohemagglutinin (PHA) or staphylococcal filtrate (SF) were observed; donors of blood lymphocytes included patients with mammary, stomach, bronchial and thyroid carcinoma, patients with Hodgkin's disease and lymphosarcoma, and patients with acute leukemia, chronic leukemia, and multiple myeloma. The responses of cancer patient lymphocytes to PHA were expressed as percentages of the response of normal cells. Lymphocytes from non-lymphoid cancer patients showed reactions to PHA in the normal range (i.e., 80-110% of the normal response); in contrast, lymphocytes from patients with lymphoid diseases showed a depressed response. Patients with chronic leukemia and lymphosarcoma showed lymphocyte responses to PHA which were in the range of 10-40% of normal. It was found that Hodgkin's disease lymphocytes showed a variable response, ranging from 5-95% of normal values. The patterns of response to SF among lymphocytes from carcinoma patients and lymphocytes from lymphoid disease patients were similar to the patterns of the PHA response. The maximal responses to PHA or SF in normal lymphocytes were recorded on the 3rd and 5th days of incubation, resp.; in contrast, lymphocytes from patients with lymphoid malignancies other than lymphosarcoma usually showed a 2-3 day delay in their response to the stimulants.

- 0482 SERUM-MEDIATED INHIBITION OF LYMPHOCYTE STIMULATION BY AUTOCHTHONOUS HUMAN TUMORS. (E.) Vanky, F. (Dept. Biol., Karolinska Inst., Stockholm, Sweden), J. Stjernswärd, G. Klein and U. Nilsson. *J Nat Cancer Inst* 47(1):95-103, 1971.

Tumor cells from sarcoma-bearing patients were treated with mitomycin C (MMC) and exposed to autochthonous

lymphocytes; the degree of lymphocyte stimulation produced by the MMC-treated tumor cells was investigated by observing the uptake of  $^3\text{H}$ -thymidine by DNA in lymphocytes. In an experiment using cells from a fibrosarcoma, the incorporation of  $^3\text{H}$ -thymidine into lymphocytes was 3 times higher in lymphocytes exposed to autochthonous MMC-treated fibrosarcoma cells than in lymphocytes incubated with similar numbers of MMC-treated autochthonous lymphocytes. However, preincubation of fibrosarcoma cells with serum from the donor of the sarcoma cells completely abolished the stimulatory effect of the tumor cells on lymphocyte  $^3\text{H}$ -thymidine uptake. In similar experiments using cells from oligodendroglioma, liposarcoma and chondrosarcoma, tumor cells stimulated lymphocyte  $^3\text{H}$ -thymidine incorporation. In 5 of 7 patients the autochthonous serum reduced  $^3\text{H}$ -thymidine uptake by lymphocytes from 54-92%. The lymphocyte stimulation-blocking effect of allogeneic sera was also tested; it was found that sera from sarcoma patients blocked the stimulation of lymphocyte  $^3\text{H}$ -thymidine uptake by cells from sarcomas from other patients. However, sera from patients with tumors other than sarcomas, and sera from healthy donors, did not block  $^3\text{H}$ -thymidine incorporation into sarcoma cells. Sera prepared from a fibrosarcoma patient prior to resection of tumor blocked  $^3\text{H}$ -thymidine uptake of autochthonous lymphocytes in the presence of tumor cells from the patient (72-93% inhibition of  $^3\text{H}$ -thymidine uptake); sera taken from the same patient 4 wk after resection of tumor were not as effective in blocking lymphocyte stimulation (24.5-39.5% inhibition of  $^3\text{H}$ -thymidine uptake).

0483 RESPONSE OF LYMPHOCYTES FROM PATIENTS WITH GASTROINTESTINAL CANCER TO THE CARCINO-EMBRYONIC ANTIGEN OF THE HUMAN DIGESTIVE SYSTEM. (E.) Lejtenyi, M. C. (McGill U. Med. Clin., Montreal, Quebec, Canada), S. O. Freedman and P. Gold. *Cancer* 28(1):115-120, 1971.

0484 HL-A ANTIGENS AND SUSCEPTIBILITY TO DISEASES: A STUDY OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA, HODGKIN'S DISEASE, AND CHILDHOOD ASTHMA. (E.) Thorsby, E. (U. Hosp., Oslo, Norway), A. Engeset and S. O. Lie. *Tissue Antigens* 1(3):147-152, 1971.

0485 DETECTION OF TUMOR-SPECIFIC CELL SURFACE ANTIGEN OF SIMIAN VIRUS 40-INDUCED TUMORS BY THE ISOTOPIC ANTIGLOBULIN TECHNIQUE. (E.) Ting, C.-C. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and R. B. Herberman. *Int J Cancer* 7(3):499-506, 1971.

0486 REGAN ISOENZYME: A CARCINOPLACENTAL ANTIGEN. (E.) Fishman, W. H. (Tufts U. Sch. Med., Boston, Mass.), N. R. Inglis and S. Green. *Cancer Res* 31(7):1054-1057, 1971.

0487 IMMUNOLOGICAL REACTIVITY OF MICE BEARING A TRANSPLANTED GARDING-PASSY MELANOMA. (Rus.) Kovalev, I. Ye. (N.I. Pirogov Med. Inst. Moscow, U.S.S.R.), V. L. Grigor'yan-Kovaleva, Ye. D. Rubtsova, A. A. Burkin, V. V. Shaydrov and I. D. Ionov. *Vop Onkol* 17(4):55-58, 1971.

0488 ABNORMAL SERUM ANTIGENS IN DIETHYLNITROSAMINE-INDUCED HEPATOMA BEARING RATS: HETEROANTIGENS, LIVER AND CARCINO-EMBRYONAL ANTIGENS. (Sp.) Alvarez-Moreno, C. (U. Navarra, Spain), J. M. Arcos, R. Martin-Rueda and A. Chordi. *Rev Esp Oncol* 16(2):105-114, 1969.

0489 MYELOMA WORKSHOP. (E.) Waldenström, J. (No affiliation) and J. V. Dacie. *Brit Med J* 2(5757):319-328, 1971.

0490 PROTECTION AGAINST SPONTANEOUS MOUSE MAMMARY ADENOCARCINOMA BY INOCULATION OF HEAT-TREATED SYNGENEIC MAMMARY TUMOR CELLS. (E.) Check, J. H. (Hahnemann Med. Coll., Philadelphia, Pa.), T. C. Childs, L. W. Brady, A. R. Derasse and K. E. Fuscaldo. *Int J Cancer* 7(3):403-408, 1971.

0491 THE EFFECT OF POLYINOSINIC:POLYCYTIDYLIC ACID ON FLUORESCENT AND NEUTRALIZING ANTIBODIES TO *Herpesvirus saimiri* IN GOATS. (E.) Fraser, C. E. O. (Harvard Med. Sch., Southboro, Mass.), L. V. Melendez, H. H. Barahona and M. D. Daniel. *Int J Cancer* 7(3):397-402, 1971.

0492 H-2 IMMUNOGENICITY OF VARIOUS TISSUE EXTRACTS AS DETECTED BY GROWTH OF AN ALLOGENEIC TUMOUR. (E.) Hilgert, I. (Czechoslovak Acad. Sci., Prague), K. Koubek and H. Kristofova. *Folia Biol (Praha)* 17(2):73-85, 1971.

See also:

- \* (Rev): 0307, 0308, 0312, 0322, 0325, 0326
- \* (Viral): 0403, 0409, 0410, 0415, 0441



# PATHOGENESIS

- 0493 RELATION BETWEEN THE PATHOLOGICAL NATURE AND THE GROWTH RATE OF HUMAN TUMORS. (E.) Charbit, A. (Gustave-Roussy Inst., Villejuif, France), E. P. Malaise and M. Tubiana. *Europ J Cancer* 7:307-315, 1971.

Statistical analyses were carried out on data reported from 538 cases of human tumors to determine whether there was a correlation between the pathological nature of specific tumors and their mean growth rate (i.e., doubling time); the reported cases included 131 patients with primary tumors and 389 with lung metastases. Tumors were divided into 5 pathological groups: squamous cell carcinomas, adenocarcinomas, malignant mesenchymal tumors, malignant lymphomas and embryonal carcinomas. Statistical analysis of data on tumor doubling time showed that primary adenocarcinomas of the breast and bronchi exhibited the slowest growth rate, followed by the squamous cell carcinomas. In both cases the primary tumors had lower growth rates than their lung metastases. Metastases of malignant sarcomatous tumors showed a faster growth rate than metastases of squamous cell carcinomas. Malignant lymphomas in the lymph nodes, lungs and s.c. tissue grew more rapidly than did pulmonary metastases of malignant sarcomatous tumors. Embryonal tumors and malignant lymphomas had the most rapid growth rates of the tumors studied.

- 0494 THE DEVELOPMENT OF EXPERIMENTAL TUMORS OF THE PERICARDIUM. (A ROENTGENOLOGICAL STUDY). (Rus.) Astapov, B. M. (Acad. Med. Sci., Moscow, U.S.S.R.), R. A. Brodskiy and Y. M. Levin. *Vop Onkol* 17(5):51-55, 1971.
- 0495 MALIGNANT POTENTIAL OF POLYPOID LESIONS OF THE COLON AND RECTUM. (E.) Horn, R. C. (Henry Ford Hosp., Detroit, Mich.). *Cancer* 28(1):146-152, 1971.
- 0496 GASTRIC JUICE DNA LEVELS IN CHRONIC GASTRITIS AND GASTRIC CANCER. (Rus.) Semenchuk, D. D. (Sci. Res. Inst. Clin. Exp. Oncol., Kiev, U.S.S.R.) *Vrach Delo* (5):74-77, 1971.
- 0497 LUNG CARCINOMA IN CHRONIC PULMONARY FIBROSIS. (Ger.) Haupt, R. (Reg. Hosp., Leipzig, Germany). *Zbl Allg Path* 114(3):295-302, 1971.
- 0498 PRECANCEROUS CONDITIONS OF THE LARYNX AND PHARYNX. (Sp.) Ager, E. (Natl. Inst. Oncol., Madrid, Spain). *Rev Esp Oncol* 16(2):49-63, 1969.

- 0499 PROLIFERATION AND DIFFERENTIATION OF NORMAL AND NEOPLASTIC CELLS IN THE COLON OF MAN. (E.) Lipkin, M. (Cornell U. Med. Coll., New York, N.Y.). *Cancer* 28(1):38-40, 1971.
- 0500 LEUKAEMIC TRANSFORMATION OF ENGRAFTED HUMAN CELLS *IN VIVO*. (E.) Fialkow, P. J. (Dept. Med. Genet., U. Washington, Seattle), E. D. Thomas, J. I. Bryant and P. E. Neiman. *Lancet* 2(7715):101-102, 1971.
- 0501 LEUKAEMIC TRANSFORMATION OF ENGRAFTED HUMAN CELLS *IN VIVO*. (E.) Goh, K. (U. Rochester Sch. Med. Dent., N.Y.). *Lancet* 2(7715):101, 1971.
- 0502 THE EFFECT OF AN ISOLATION-INDUCED STRESS ON THE DEVELOPMENT OF ASCITIC TUMOR IMPLANTS IN MICE. THE ROLE OF THE ADRENALS. (Fr.) Dechambre, R. P. (Gustave-Roussy Inst. Animal Exp., Villejuif, France), and C. Gosse. *C R Acad Sci* 272:2720-2722, 1971.
- 0503 PROSTATIC CANCER: GENERALISED MALIGNANT PATTERN OF LACTATE DEHYDROGENASE ISOENZYMES. (E.) Oliver, J. A. (Royal Victoria Hosp., Montreal, Quebec, Canada) and A. M. Abdalla. *Brit J Urol* 43(3):321-323, 1971.
- 0504 MINUTE ADENOMATOUS AND HYPERPLASTIC POLYPS OF THE COLON: DIVERGENT PATTERNS OF EPITHELIAL GROWTH WITH SPECIFIC ASSOCIATED MESENCHYMAL CHANGES: CONTRASTING ROLES IN THE PATHOGENESIS OF CARCINOMA. (E.) Lane, N. (Columbia U. Coll. Phys. Surg., New York, N.Y.), H. Kaplan and R. R. Pascal. *Gastroenterology* 60(4):537-551, 1971.
- 0505 CYSTITIS GLANDULARIS AND ADENOCARCINOMA OF THE BLADDER. (E.) Susmano, D. (VA Hosp., Hines, Ill.), A. B. Rubenstein, A. R. Dakin and F. A. Lloyd. *J Urol* 105(5):671-674, 1971.
- 0506 THE ULTRASTRUCTURE OF RETINOBLASTOMA. (Hun.) Lapis, K. (Sote J. Inst., Budapest, Hungary) and M. Radnot. *Magy Onkol* 15(1):11-23, 1971.
- 0507 SCAR CARCINOMAS OF THE ESOPHAGUS. (Ger.) Imre, J. (Szeged Med. Sch., Hungary) and M. Gergely. *Thoraxchirurgie* 19(3):181-187, 1971.

See also:

\* (Rev): 0317, 0322

- 0508 CERUMEN GENETICS AND HUMAN BREAST CANCER (E.) Petrakis, N. L. (G. W. Hooper Fdn., U. California, San Francisco). *Science* 173(3994):347-349, 1971.

A correlation is established between mortality and frequency rates of mammary carcinoma and possession of the genetic allele for wet cerumen (earwax); it has been shown that cerumen occurs in 2 phenotypic forms, wet and dry, and that the quality of cerumen is controlled by a single pair of genes in which the allele for wet cerumen is dominant. The frequency of the wet gene is high in Caucasians and in U.S. and African Negroes, while the wet allele is more uncommon in Mongoloid peoples, both in Asia and in the Americas. In a survey of statistics from 24 population groups distributed throughout the world it was found that breast cancer mortality and case frequency correlated positively with frequency of wet cerumen. In populations in which the frequency of wet cerumen approached 1 (U.S. Whites and Negroes) the mortality from breast cancer approached 20 deaths/100,000 population, while in populations in which the frequency of wet cerumen was less than 0.20 (Japanese in California and Japan) the mortality from breast cancer was 5 deaths/100,000 population or less. In a study of Japanese breast cancer patients in California, it was found that 9 of 31 breast cancer patients had wet cerumen while 9 of 52 healthy Japanese women had wet cerumen. This finding suggested that Japanese women with wet cerumen are more likely to develop breast cancer than Japanese women with dry cerumen. Since the ceruminous glands and the mammary glands are both of the apocrine type, it is suggested that the apocrine system's genetically determined variation may influence susceptibility to breast cancer.

- 0509 GEOGRAPHIC PATHOLOGY OF CANCER OF THE COLON AND RECTUM. (E.) Stewart, H. L. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.). *Cancer* 28(1):25-28, 1971.

Geographic differences in the prevalence of cancer of the colon and rectum are discussed; data indicate that colonic and rectal cancers are caused by carcinogenic agents in the human environment, not by genetic factors of the respective racial groups. The highest rates for both colonic and rectal cancer are generally found in English-speaking nations and in industrialized areas (with the notable exception of Japan, an industrial nation which has low incidence rates for both conditions). South American countries have low rates of colonic and rectal cancer; the lowest rates for these conditions are found in Africa south of the Sahara. No satisfactory explanation for this has been advanced. The incidence of rectal cancer is usually less than that of colonic cancer. Both cancer of the colon and cancer of the rectum are slightly more prevalent among females than among males. The importance of environment, in contrast to race, in the etiology of cancer of the colon and rectum is demonstrated by the high rates of both conditions for Japanese, Negroes

and Chinese living in the United States; in Japan, sub-Saharan Africa, and China, rates for both conditions are low.

- 0510 POPULATION SURVEYS ON THE PREVALENCE OF THYROID CANCER IN A NON-ENDEMIC REGION, NAGANO, JAPAN. (E.) Maruchi, N. (Fac. Med., U. Tokyo, Japan), R. Furihata and M. Makiuchi. *Int J Cancer* 7(3):575-583, 1971.

In the period 1965-1970, a survey was carried out on the incidence of thyroid disease, including thyroid carcinoma, in the Nagano Prefecture near Tokyo, Japan, an area in which thyroid carcinoma is non-endemic. In a total population of 73,045 there were 2,098 cases of thyroid disease (goiter); 1,730 of these cases were females. The incidence of the various types of goiter was not sex-dependent. There were 633 cases of nodular goiter, a condition which has a strong clinical association with thyroid carcinoma. In both sexes, the incidence of nodular goiter increased with age. Seventy-six cases of thyroid carcinoma were observed (60 females and 16 males), yielding a prevalence rate of 1.3 cases of thyroid carcinoma/1,000 subjects (0.6 for males and 1.9 for females). The incidence of thyroid carcinoma increased with age for both sexes; there were more cases among persons over 30-year-old than among persons in the under 30-year-old age group. Seventy-four percent of thyroid carcinoma cases were diagnosed as "stage I carcinoma" (i.e., disease confined to the thyroid with no metastases), and 21% of cases were diagnosed as "stage III" (i.e., primary carcinoma in the thyroid with metastases in cervical lymph nodes). Within the Nagano Prefecture there was some regional variation in the incidence of thyroid carcinoma among females; there was no significant regional variation in thyroid carcinoma incidence among males. As in other regions, the mortality from thyroid carcinoma in the Nagano Prefecture was low in comparison to its incidence.

- 0511 ASSOCIATION BETWEEN AFLATOXIN CONTENT OF FOOD AND HEPATOMA FREQUENCY IN UGANDA. (E.) Alpert, M. E. (Massachusetts Gen. Hosp., Boston), M. S. R. Hutt, G. N. Wogan and C. S. Davidson. *Cancer* 28(1):253-260, 1971.

The distribution of aflatoxins in foods stored for consumption was correlated with the pattern of incidence of liver cancer in Uganda. Foodstuffs stored and subject to aflatoxin contamination included beans, maize, sorghum and groundnuts; 71.9% of bean samples were found to be contaminated by aflatoxin. Aflatoxin in amounts exceeding 1 µg/kg was found in 29.6% of food samples and aflatoxin in amounts exceeding 1 mg/kg was found in 3.7% of



food samples. In 2 districts of Uganda, Karamoja and Toro, the aflatoxin content in stored foods was found to be especially high; 51.5% (mean) of samples from these regions were contaminated by aflatoxin. In 4 other provinces of Uganda, 20.9% of food samples were found to contain some aflatoxin. There appeared to be a correlation between aflatoxin contamination of stored foods and incidence of hepatoma. The highest incidence of hepatoma (15 cases/100,000 population/yr) was found in the Karamoja district, where the frequency of aflatoxin contamination of stored foods was high. In other districts, where aflatoxin contamination of foods was less frequent than in Karamoja, the incidence of hepatoma ranged from 1.4-3.0 cases/100,000 population/yr.

- 0512 EPIDEMIOLOGY OF CANCER OF THE PROSTATE. (E.) Wynder, E. L. (American Hlth. Fdn., New York, N.Y.), K. Mabuchi and W. F. Whitmore, Jr. *Cancer* 28(2):344-360, 1971.

An investigation of the epidemiology of cancer of the prostate was carried out based upon information from 300 patients with cancer of the prostate and 400 controls, hospital records of an additional 350 patients with prostate cancer, and a review of the literature. Incidence data reveal a low rate of prostatic cancer among Jewish men in the United States. This appears related to the lower rate of prostatic cancer among immigrants from Eastern Europe. Native-born Jews appear to have rates similar to those of other Caucasians born in the United States. The present study shows no significant correlation of rate with marital status or fertility. No differences are seen in educational level between the cancer and control groups. Tobacco and alcohol habits of prostatic cancer patients are similar to those of the control patients. Surgical and medical histories of prostatic cancer patients reveal no unusual disease patterns compared with controls. Additional data is required on prostatitis before its possible effect on prostatic cancer can be evaluated. No differences were found between cancer and control groups with respect to circumcision, weight, height, blood group, or hair distribution. The rarity of clinical prostatic cancer in Japan and its increase among first generation Japanese immigrants in the U.S. is noted.

- 0513 EPIDEMIOLOGIC EVIDENCE FOR MULTI-STAGE THEORY OF CARCINOGENESIS. (E.) Hakama, M. (Finnish Cancer Reg., Helsinki). *Int J Cancer* 7(3):557-564, 1971.

A multi-stage mathematical model of carcinogenesis is proposed assuming time homogeneous transition intensities from stage to stage. The model shows a fairly close agreement with the observed age incidence curves, not only for epithelial tumors, but also for tumors showing a more irregular age pattern. The model is applied to study the mechanisms of carcinogenesis. Selected primary sites are considered which represent different types of age incidence patterns. It is proposed that tumors of peripheral nerves in children and

young adults are a result of a single change. Acute leukemia in children is suggested to be a result of two discrete events, whereas most tumors of epithelial origin require several changes. Tumors with a bimodal incidence curve, like Hodgkin's disease and breast cancer, are likely to consist of two entities. It is stressed that the assumption of constant transition intensities may not be true, especially in regard to tumors with conceivably long periods of exposure.

- 0514 SEXUAL FACTORS IN THE EPIDEMIOLOGY OF CANCER OF THE PROSTATE. (E.) Steel, R. (Dept. Comm. Hlth, Queen's U., Kingston, Ontario, Canada), R. E. M. Lees, A. S. Kraus and C. Rao. *J Chronic Dis* 24:29-37, 1971.

Thirty-nine patients with prostatic carcinoma treated in Kingston, Ontario, hospitals were matched with 39 controls (e.g., patients without genito-urinary disease and without carcinoma) and with 35 patients with benign prostatic hyperplasia (BH). The variations in social and medical parameters among the 3 groups were observed. Among prostatic carcinoma patients, 12.8% had a history of prostatic carcinoma in a father or brother; family history of prostatic carcinoma was found in 5.1% of controls and in 20% of BH patients. A history of venereal disease was found in 12.8% of carcinoma patients, in 2.5% of controls, and in 5.7% of BH patients. Prostatic carcinoma patients had sexual intercourse more than 3 times/wk in 53.9% of cases; a thrice weekly frequency of sexual intercourse was found in 71.8% of controls and in 34.3% of BH patients. In interviews, 21% of carcinoma patients indicated a desire for more sexual activity than they had had, while none of the controls and 5.8% of the BH patients desired increased sexual activity. Among prostatic carcinoma patients, 34.2% had 6 or more sexual partners before and/or after marriage, while 10.5% of controls and 8.8% of BH patients had had 6 or more sexual partners. Contraceptives were used by 33.3% of carcinoma patients, by 2.5% of controls and by 14.2% of BH patients.

- 0515 LEUKEMIA AND LYMPHOMA IN CALI, COLOMBIA: EPIDEMIOLOGICAL CONSIDERATIONS. (Sp.) Guzman, N. G. (Cali U., Colombia) et al. *Boletín Sanit Panam* 71(1):41-49, 1971.

The incidence of leukemia, lymphosarcoma and other lymphoma, Hodgkin's disease and multiple myeloma was investigated in Cali. The analysis was based upon data provided by cancer incidence records for 1962 to 1966. The annual incidence of leukemia (including all cytological types) was found to be 3.2 per 100,000 with a male/female ratio of 2:1. This ratio appeared to be 3 times higher for the population group below 5-yr-old. A peak incidence of leukemia in males was seen in the 1-4 yr-old group; a minor decrease was observed between 25 and 35 yr of age and another peak occurred during the last decades of life. Acute leukemia was found to be more frequent than chronic leukemia below 15 yr-of-age. A peak incidence of lymphoma was seen in the population

group below 25 yr-of-age. The incidence of Hodgkin's disease showed 2 peaks among the male population, one between 5 and 14-yr-old and the other between 45 and 64-yr-old; the male/female ratio within the group below 15 yr-of-age appeared to be 12:1. Multiple myeloma showed an incidence of 6 cases/million population/yr. Sex-related differences in the incidence of lymphoproliferative diseases appeared to indicate a higher susceptibility in males to unknown leukemogenic factors rather than a difference in environmental exposure.

- 0516 IgE MYELOMA: TOTAL BODY TUMOR CELL NUMBER AND SYNTHESIS OF IgE AND DNA. (E.) Salmon, S. E. (U. California Sch. Med., San Francisco), O. R. McIntyre and M. Ogawa. *Blood* 37(6):696-705, 1971.

Tritiated thymidine incorporation by IgE myeloma cells, synthesis of IgE, and tumor cell number were established in a 60-yr-old male with IgE myeloma; values were compared with those found in patients with IgG myeloma. After labeling of bone marrow cells with  $^3\text{H}$ -thymidine, heavy labeling was noted in the nuclei of 13% of the IgE myeloma cells. The maximum percentage of bone marrow cell nuclei to incorporate labeling was 3.8% among 5 IgG myeloma patients. However, the labeling index of  $^3\text{H}$ -thymidine for blood cells of a patient with light chain myeloma and plasma cell leukemia was 40%. The rate of cellular secretion of IgE in myeloma cells was 26,000 molecules of IgE/min; this rate was similar to the rate of cellular secretion of IgG in patients with IgG myeloma. The total body myeloma cell number of the IgE myeloma patient was  $2.7 \times 10^{12}$  cells and for the IgG myeloma patient,  $3.1 \times 10^{12}$  cells. Over the clinical course of the patient's disease (which lasted 1 yr) the number of myeloma cells dropped from a maximum of  $3.6 \times 10^{12}$  to a minimum of  $1.5 \times 10^{12}$  at 1 month, and thereafter increased steadily, reaching  $3 \times 10^{12}$  at the time of the patient's death.

- 0517 RADIOLOGICAL METHODS FOR THE EARLY DIAGNOSIS AND FOLLOW-UP OF EXPERIMENTALLY INDUCED TUMORS IN RAT AND MOUSE. (Ger.) Bürkle, G. (Radiol. Inst., U. Tübingen, Germany), J. Sander, V. Bürkle and W. Vergau. *Fortschr Roentgenstr* 114(5):698-710, 1971.

- 0518 INCIDENCE OF MENINGIOMA OF THE POSTERIOR CEREBRAL FOSSA IN INTRA-CRANIAL TUMOR PATHOLOGY. (Fr.) Lecuire, J. (No affiliation), Y. P. Dechaume. *Neurochirurgie* 17(Suppl. 2):17-26, 1971.

- 0519 TESTICULAR TUMORS OBSERVED IN A GERMAN ARMY UNIT. (Fr.) Mairose, U. B. (Barmbeck Gen. Hosp., Hamburg, Germany), Y. E. Altwein and K. Wegner. *Bull Cancer* 58(1):103-114, 1971.

- 0520 LEUKEMIA IN BLACK AFRICA. (Fr.) Linhard, J. (No affiliation) and B. Diop. *Med Afrique Noire* 18(4):351-358, 1971.

- 0521 CANCER OF THE GASTROINTESTINAL TRACT IN AFRICA AT DAKAR. (Fr.) Chabal, J. (Dakar Med. Sch., Senegal), V. M. Vovor, B. Dionf and P. Toure. *Med Afrique Noire* 18(4):361-367, 1971.

- 0522 THE EPIDEMIOLOGY OF TUMORS AMONG CHILDREN IN HUNGARY. (Hun.) Rode, I. (Natl. Inst. Oncol., Budapest, Hungary). *Magy Onkol* 15(1):3-10, 1971.

- 0523 GROWTH OF METASTASES FROM P-388 SARCOMA IN THE RAT FOLLOWING WHOLE BODY IRRADIATION. (E.) Van Den Brenk, H. A. S. (St. Thomas' Hosp., London, England), V. Moore and C. Sharplington. *Brit J Cancer* 25(1):186-207, 1971.

- 0524 CUTTING OILS AND CANCER. (E.) Waterhouse, J. A. H. (Queen Elizabeth Hosp., Birmingham, England) *Ann Occup Hyg* 14:161-170, 1971.

- 0525 PRELIMINARY REPORT OF THE INCIDENCE OF CERVICAL CARCINOMA *IN SITU* IN IRAQ. (E.) Kubba, K. (Med. Res. Ctr., U. Baghdad, Iraq). *Acta Cytol* 15(2):171-172, 1971.

- 0526 CARCINOMAS AND MALIGNANT MELANOMAS OF THE SKIN IN WESTERN INDIA. (E.) Paymaster, J. C. (Tata Mem. Ctr., Bombay, India), G. V. Talwalkar and P. Gangadharan. *J Roy Coll Surg Edinb* 16(3):166-173, 1971.

- 0527 FEEDBACK REGULATION OF GROWTH OF ASCITES TUMOURS IN PARABOTIC MICE. (E.) Bichel, P. (Cancer Res. Inst., Aarhus, Denmark). *Nature* 231(5303):449-450, 1971.

- 0528 MUTATION AND CANCER: STATISTICAL STUDY OF RETINOBLASTOMA. (E.) Knudson, A. G., Jr. (Grad. Sch. Biomed. Sci., U. Texas, Houston). *Proc Nat Acad Sci USA* 68(4):820-823, 1971.

- 0529 AN ANTHROPOMETRIC STUDY OF WOMEN WITH CANCER. (E.) Brinkley, D. (Dept. Human Ecol., U. Cambridge, Cambridge, England), R. G. Carpenter and J. L. Haybittle. *Brit J Prev Soc Med* 25(2):65-75, 1971.

- 0530 TOXIC ADENOMA IN NORTHERN GREECE: SCINTIGRAPHIC, HISTOLOGICAL AND EPIDEMIOLOGICAL STUDY. (Gr.) Apostolidis, P. (Thergion Cancer Inst., Thessaloniki, Greece), A. Deconomou and N. Kostaki. *Hell Iatriki* 40(2):144-155, 1971.



0531 MORTALITY FROM CANCER OF THE LARYNX IN THE UKRAINIAN S.S.R. (1955-1968). (Rus.) Perebatova, M. A. (Res. Inst. Otolaryngol., Kiev, U.S.S.R.) *Zh Ushn Nos Gorl Bolez* 31(3):23-27, 1971.

0532 POST-CRICOID CARCINOMA AND THE PATERSON-KELLY SYNDROME. (E.) Richards, S. H. (Roy. Infirm., Cardiff, Wales), D. Kilby and J. D. Shaw. *J Laryng* 85(2):141-152, 1971.

0533 EPIDEMIOLOGY OF CANCER OF THE COLON AND RECTUM. (E.) Burkitt, D. P. (London, England). *Cancer* 28(1):3-13, 1971.

0534 EVALUATION OF CANCER RISK IN TOBACCO CHEWERS AND SMOKERS: AN EPIDEMIOLOGIC ASSESSMENT. (E.) Jussawalla, D. J. (Bombay Cancer Registry, India) and V. A. Deshpande. *Cancer* 28(1):244-252, 1971.

See also:

\* (Rev): 0301, 0317, 0320, 0323, 0331, 0333

# MISCELLANEOUS

- 0535 CARCINOMA OF NASOPHARYNX IN TWINS. (E.) Nevo, S. (Rambam Govt. Hosp., Haifa, Israel), W. Meyer and M. Altman. *Cancer* 28(3):807-809, 1971.

Nasopharyngeal carcinoma was reported in each of 2 male dizygotic twins; the twins, born in Morocco in 1946, emigrated to Israel in 1956. They were the youngest of 10 siblings; there was evidently no consanguinity in the family. Carcinoma of the nasopharynx was diagnosed in the twins in 1967 and 1968. One carcinoma was a fungating tumor located in the right vault of the nasopharynx and the other was an anaplastic squamous cell carcinoma located above the right tubal ostium. Both tumors remitted following treatment with telecobalt irradiation. This case was thought to be the first instance on record of nasopharyngeal carcinoma in twins.

- 0536 LOSS OF FEEDBACK CONTROL OF HYDROXYMETHYL-GLUTARYL COENZYME A REDUCTASE IN HEPATOMAS. (E.) Siperstein, M. D. (U. Texas Med. Sc., Dallas), A. M. Gyde and H. P. Morris. *Proc Nat Acad Sci USA* 68(2):315-317, 1971.

Minimal-deviation Morris hepatomas 9121 and 3924A were grown i.m. in rats maintained on a 5% cholesterol diet and the hydroxymethylglutaryl coenzyme mevalonate reductase (HMG-CoA) of liver microsomes prepared from normal and tumor-bearing cholesterol-fed rats was assayed. Evidence was found that the cholesterol feedback lesion in cancer is localized to the enzyme mevalonate: NADP oxidoreductase (acylating CoA) (i.e., hydroxy-methylglutaryl CoA reductase). Cholesterol feeding reduced the activity of HMG-CoA reductase in normal rat liver by 90%; HMG-CoA reductase in livers of rats not fed cholesterol measured 0.77 nmol/sample/hr while HMG-CoA reductase in rats fed with 5% cholesterol diets measured 0.007 nmol/sample/hr. Cholesterol failed to decrease HMG/CoA reductase activity in hepatoma tissue. In hepatoma 9121-bearing rats given cholesterol, HMG-CoA reductase measured 1.69 nmol/sample/hr and in hepatoma 3924-bearing rats given cholesterol HMG-CoA reductase measured 4.5 nmol/sample/hr.

- 0537 CALCIUM METABOLISM IN TUMORS: ITS RELATIONSHIP WITH CHROMIUM COMPLEX ACCUMULATION: I. UPTAKE OF CALCIUM AND PHOSPHORUS BY EXPERIMENTAL TUMORS. (E.) Anghileri, L. J. (Med. Ctr., U. Colorado, Denver) and E. S. Miller. *Oncology* 25(2):119-136, 1971.

Mice of various strains bearing s.c. implanted tumors of various types were given i.p. injections of radioactive calcium ( $^{45}\text{Ca}$ ) or radioactive phosphorus ( $^{32}\text{P}$ ) and the uptake of the labels by tumor tissues was observed; tumors included hepatoma (on C57L/J mice), Ehrlich carcinoma (albino mice), lymphatic leukemia (AKR/J mice), lymphosarcoma (C3H/HeJ mice) and melanoma (C57BL/6J mice). Labeled tumor tissue, as well as other tissue samples, was fractionated by successive treatments with ethanol, ethyl ether, water, acetic acid and hydrochloric acid. Except for melanoma, calcium uptake was greater in tumor tissue than in other tissues. In all cases, normal, non-tumor-bearing mice incorporated less calcium in tissues than tumor-bearing mice. Thus, hepatomas in C57L/J

mice incorporated 1.31  $\mu\text{g}$  of Ca/g tissue whereas other organs did not exceed 0.393  $\mu\text{g}$  Ca/g tissue. Further, in hepatoma-bearing mice liver and kidney incorporated, resp., 0.100 and 0.154  $\mu\text{g}$  Ca/g tissue versus 0.076 and 0.087  $\mu\text{g}$  Ca/g tissue in non-tumor-bearing mice. Ca in tumor tissue was incorporated mainly in the acetic acid-soluble fractions of tissue; however, in older necrotic tumors (i.e., 25-day-old tumors) Ca often became concentrated in the hydrochloric acid-soluble fraction. Phosphorus was incorporated mainly in the hydrochloric acid-soluble fractions of tumor tissues. In lymphatic leukemia and lymphosarcoma-bearing mice there was a general increase in the hydrochloric acid-soluble fraction; it was found that the increase in tumor size was generally accompanied by a reduction in the acetic acid-soluble fraction and an increase in the hydrochloric acid-soluble fraction.

- 0538 CALCIUM METABOLISM IN TUMORS: ITS RELATIONSHIP WITH CHROMIUM COMPLEX ACCUMULATION: II. CALCIUM, MAGNESIUM AND PHOSPHORUS IN HUMAN AND ANIMAL TUMORS. (E.) Anghileri, L. J. (U. Colorado Med. Ctr., Denver), E. S. Miller, J. Robinette, K. N. Prasad and V. A. Lagerborg. *Oncology* 25(3):193-209, 1971.

Animal and human tumors were assayed for concentrations of calcium (Ca), phosphorus (P) and magnesium (Mg); concentrations of elements in tumor tissue were compared with concentrations in organs. Animal tumors examined included Ehrlich carcinoma, melanoma, lymphosarcoma, lymphatic leukemia and hepatoma. In animal tumors, the highest concentrations of Ca were found in lymphatic leukemia (3.71  $\mu\text{g/g}$  wet tissue) and lymphosarcoma 0.85  $\mu\text{g/g}$  wet tissue; Ca concentrations in the tumors generally were 1.5-3.0 times higher than concentrations of Mg. Soluble Ca usually comprised less than 50% of total Ca in tumor tissue; however, in lymphatic leukemia, soluble Ca made up 85% of total Ca. In all tumors save melanoma, Ca and Mg were more highly concentrated in tumor tissue than in liver and kidneys. The tumor and organ distribution of Ca appeared to be distinctive in each type of tumor. Total P did not vary greatly from one type of tumor to another, and the pattern of P distribution was usually similar in tumor tissue and in organs. When uptake of radioactive Ca and P by tumor tissue was compared with the concentrations of Ca and P in tumor tissue, it was found that, in tumors other than lymphatic leukemia, the percentage of total Ca present in the C fraction of tumor tissue was lower in the  $^{45}\text{Ca}$  uptake than in the chemical Ca concentration determination. Total Ca in human tumors (including kidney adenocarcinoma, lung carcinoma, liver sarcoma and breast carcinoma) was equal to or higher than that in normal human tissue. Concentrations of P and Mg in human tumors varied more widely than did concentrations of Ca.

- 0539 EPITHELIAL BODIES IN SECONDARY HYPERPARATHYROIDISM AND IN PRIMARY ADENOMA IN HUMANS: ULTRASTRUCTURAL COMPARISON. (Ger.) Altenähr, E. (Inst. Pathol. U. Hamburg, Germany) and G. Seifert. *Virchow Arch Path Anat* 353(1):60-86, 1971.

The ultrastructure of human parathyroids from 3



patients with parathyroid adenoma, from 3 patients with secondary hyperparathyroidism and from 3 control subjects was investigated. The normal parathyroids revealed several types of electron dense granules, (considered to be prosecretory or secretory granules), complex lipid bodies and numerous lipid vacuoles. The activated cells of secondary hyperparathyroidism-associated epithelial bodies revealed ultrastructural alterations such as increased glycogen levels, enlargement of the Golgi apparatus, increased amounts of prosecretory granules, a spread of rough surfaced endoplasmic reticulum, a decrease in lipid vacuoles and an increased sinuosity of the cell membranes. The specimens from parathyroid adenomas revealed irregular cytoplasmic organelles and irregularly-shaped nuclei; the Golgi apparatus appeared to be poorly developed and the shape and size of the electron dense granules appeared to be different from those found in the normal or hyperplastic gland specimens. Annulate lamellae were observed in one of the 3 adenomas; they were considered to constitute pathological precursors of the endoplasmic reticulum.

0540 GENES FOR NEURONAL PROPERTIES EXPRESSED IN NEUROBLASTOMA x L CELL HYBRIDS. (E.)

Minna, J. (Natl. Heart Lung Inst., Natl. Inst. Hlth., Bethesda, Md.), P. Nelson, J. Peacock, D. Glazer and M. Nirenberg. *Proc Nat Acad Sci USA* 68(1):234-239, 1971.

A microelectrode technique was used to examine the electrical membrane excitability of L cells from strain C3H/AN mice, of mouse neuroblastoma cells, and of L cell-neuroblastoma cell hybrids produced by fusing L cells and neuroblastoma cells with inactivated Sendai virus. Cells showed 4 types of responses to electrical stimuli: 1. a stimulus elicited smoothly rising uninflected change in membrane voltage (designated  $A-B^-$  or passive response); 2. a stimulus elicited negatively inflected change in membrane voltage late in the response of the cell to the stimulus (designated B); 3. a stimulus elicited increase in rate of voltage change early in the membrane response to stimulus (designated A); 4. a stimulus elicited a previously undescribed response in which a large (200-400 mV) increase in membrane electrical potential was followed, after the stimulus was withdrawn, by a second increase in potential (designated C). Neuroblastoma cells exhibited the  $A-B^-$  response, the B response or the A response; no neuroblastoma cells exhibited the C response. No L cells showed either the A or B response; all were passive. However, nearly all L cells showed the C response. It was concluded that the A and B responses were neuroblastoma markers while the C response was an L cell marker. Neuroblastoma-L cell hybrids tested 20-40 generations after fusion with Sendai virus exhibited the A or the B response in all cases except one; the incidence of cells showing the A or B response equalled or exceeded the incidence of A- or B-responsive cells found in neuroblastoma parent cells. The C response was also found in cells from all the hybrid cell clones. It was concluded that at least some of the genetic information determining neuron differentiation was functionally expressed in neuroblastoma-L cell hybrid cells.

0541 DEPENDENCE OF CHROMOSOME PULVERIZATION IN VIRUS-FUSED CELLS ON EVENTS IN THE G2 PERIOD. (E.) Matsui, S. (Roswell Park Mem. Inst., Buffalo, N.Y.), H. Weinfeld and A. A. Sandberg. *J Nat Cancer Inst* 47(2):401-408, 1971.

The synthesis of a factor (PF) responsible for pulverization of chromosomes in cells fused by Sendai virus was investigated. Hamster cells were fused by exposing them to Sendai virus; simultaneously, cells were exposed to 2 protein synthesis inhibitors: puromycin or cycloheximide. When frequencies of cells showing chromosome pulverization were noted 45 min later, it was found that the pulverization frequency was not diminished by comparison to fused cells not treated with protein synthesis inhibitors; 25 min after fusion, the pulverization frequency in untreated cells was 80% and pulverization frequencies in cells treated with puromycin or cycloheximide were 75 and 85%, resp. This indicated that during metaphase, the fused cells did not synthesize PF. When virus was added to cells after treatment of cells with puromycin or cycloheximide pulverization frequencies were depressed by about 50% of the frequencies found in cells in which virus-fusion and protein synthesis inhibitor-treatment occurred simultaneously. It was estimated that the synthesis of PF in cells was completed about 15 min before the onset of cell metaphase; the time-course of chromosome pulverization inhibition by protein synthesis inhibitors suggested that the synthesis of PF begins in the G2 phase, about 45 minutes before the onset of metaphase. It was found that pulverization frequencies were relatively low in cell cultures in which large numbers of cells in mitosis had accumulated in the presence of protein synthesis inhibitors. Pulverization frequencies were also low in multinucleate cells containing 1 intact metaphase nucleus and 3 or more interphase nuclei.

0542 POLYADENYLIC ACID SEQUENCES IN THE HETEROGENEOUS NUCLEAR RNA AND RAPIDLY-LABELED POLYRIBOSOMAL RNA OF HeLa CELLS: POSSIBLE EVIDENCE FOR A PRECURSOR RELATIONSHIP. (E.) Edmonds, M. (Dept. Biochem., U. Pittsburgh, Pa.), M. H. Vaughan, Jr. and H. Nakazato. *Proc Nat Acad Sci USA* 68(6):1336-1340, 1971.

RNA from fractionated HeLa cells was analyzed by sedimentation and electrophoresis on acrylamide gels; polyadenylate sequences (poly (A)) found in rapidly-labeled polydisperse nuclear RNA (HnRNA) were characterized. Poly(A) sequences recovered from all size classes of HnRNA were similar in electrophoretic mobility; this size uniformly suggested that HnRNA molecules contain a covalently linked poly(A) sequence. Competition experiments indicated that poly(A) was not adventitiously bound to large (i.e., greater than 45S) HnRNA. Poly(A) sequences made up 0.49% of large HnRNA. Poly(A) sequences were also found in cytoplasm of HeLa cells; this poly(A) material was found in the polyribosomal fraction of cytoplasmic messenger RNA. Treatment of HeLa cell RNA with actinomycin D (5 µg/ml) reduced total RNA synthesis by 90% and

reduced poly(A) synthesis by the same amount. The findings were thought to suggest that HnRNA is a precursor of cytoplasmic messenger RNA; on this hypothesis, the HnRNA molecule contains a sequence of potential messenger RNA adjacent to a small poly(A) sequence. During transcription, the HnRNA molecule would be rapidly degraded and only a small portion of the HnRNA (a portion which includes the poly(A) sequence) would be transported to the cytoplasm.

- 0543 AMINOACYL TRANSFER RNA PROFILES IN HUMAN MYELOMA CELLS. (E.) Fujioka, S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and R. C. Gallo. *Blood* 38(2):246-252, 1971.

Transfer RNA was isolated from lymphocytes of 1 normal human subject and from a patient with multiple myeloma; the myeloma line of cells produced  $\lambda$ -type light chain protein. The aminoacyl patterns of tRNA from the 2 subjects were compared by column co-chromatography. Aspartyl-tRNAs in normal and myeloma cells showed minor differences; both cell lines showed an early-eluting small peak, a second smaller peak and a major peak, but myeloma cells had an additional late-eluting peak which normal cells lacked. Normal and myeloma cells showed similar chromatographic patterns of leucyl-tRNA and seryl-tRNA. The most conspicuous differences between the aminoacyl tRNA patterns of normal and myeloma cells were found in the tyrosyl-tRNA patterns. Myeloma cells contained 4 or 5 isoaccepting peaks for tyrosyl-tRNA; none of these peaks corresponded to the peaks of tyrosyl-tRNA eluted from normal cells.

- 0544 L-GLUTAMINE:D-FRUCTOSE 6-PHOSPHATE AMIDOTRANSFERASE IN TUMORS AND THE LIVER OF TUMOR-BEARING ANIMALS. (E.) Kikuchi, H. (Res. Inst. Tuberculosis, Leprosy and Cancer, Tohoku U., Sendai, Japan), Y. Kobayashi and S. Tsuki. *Biochim Biophys Acta* 237(3):412-421, 1971.

Levels of L-glutamine:D-fructose 6-phosphate amidotransferase were assayed in normal rat and dd mouse tissues and in tissues of animals bearing Yoshida sarcoma or AH-130 ascites hepatoma. Assays of amidotransferase activities in 105,000 g supernatants of normal rat tissue showed that the greatest enzyme activity was concentrated in liver; in tumor-free rats amidotransferase activity in liver was 24.6 U/mg protein while in brain, which had the next highest level of amidotransferase, the enzyme activity was 9.4 U/mg protein. Enzyme levels in liver of Yoshida sarcoma-bearing rats were significantly higher than enzyme levels in the livers of normal rats (amidotransferase activity in tumor-bearing rat liver was 35.2 U/mg protein). Following the implantation of Yoshida sarcoma in rats, the amidotransferase activity level rose by day 4-5 postimplantation to 167% of control enzyme levels. Thereafter, amidotransferase levels in tumor-bearing rats declined. Seromucoid levels also rose in plasma of tumor-bearing rats. Rats bearing AH-130 sarcoma showed no increase in liver amidotransferase activity in the period of tumor growth following implantation of the tumor. Amidotransferase activities were at a higher level

in tissues taken from Yoshida tumors or AH-130 tumors than in liver from tumor-free rats; Ehrlich ascites tumors from mice also had higher levels of enzyme activity than liver from tumor-free mice. Tumor extracts were found to contain an amidotransferase-specific inhibitor; normal liver extracts lacked this inhibitor.

- 0545 RNA AND PROTEIN SYNTHESIS IN PROLIFERATING AND NON-PROLIFERATING BLAST CELLS OF HUMAN ACUTE LEUKAEMIA. (E.) Chan, B. W. B. (Dept. Med., U. Cambridge, England). *Acta Haemat* 45(2):82-88, 1971. England). *Acta Haemat* 45(2):82-88, 1971.

Blast cells from blood or bone marrow of patients with acute myeloid or acute lymphoblastic leukemia were incubated with  $^3\text{H}$ -thymidine; the sizes of  $^3\text{H}$ -labeled and unlabeled blast cells were compared. In all cases, labeled cells were significantly larger than unlabeled cells; the diameters of labeled cells ranged from 11.99-12.80  $\mu\text{m}$ , while the diameters of unlabeled cells ranged from 9.82-10.41  $\mu\text{m}$ . This finding suggested that cell size could serve as a criterion for distinguishing proliferative from nonproliferative blast cells. Large proliferative blast cells were found to have a higher rate of RNA synthesis, and to synthesize more labile RNA, than smaller nonproliferative cells.

- 0546 DNA AND SEX CHROMATIN IN HUMAN SKIN TUMORS. (Rus.) Naleskina, L. A. (Kiev Res. Inst. Exp. Clin. Oncol., U.S.S.R.) *Vop Onkol* 17(4):8-14, 1971.

The morphology of nuclear chromatin, and the DNA and sex chromatin levels in 47 benign nevi, 10 malignant nevi and 88 malignant melanomas (of 100 female and 45 male patients aged 4-82-yr-old) were investigated on Feulgen-stained samples. DNA was measured at 540 m $\mu$  utilizing a specially designed cytophotometer for adsorption photometry in the visible range. The amount of DNA corresponding to a haploid set of chromosomes (1.8 conventional U) from testicle spermatis obtained from normal subjects was considered as a standard for the determination of chromosomal sets in the neoplastic preparations. The nuclei from nevus elements elicited micro-loop-like granulous chromatin structures; their DNA levels were approximately 3.5 conventional U, corresponding to the diploid chromosome set. Sex chromatin material of nevus nuclei from 28 female patients constituted 67% and ranged between 50 and 86%. The chromatin structure of elements from melanoma elicited condensed granularity, increased DNA concentrations (5-8 conventional U) and a higher degree of polyploidy. The average sex chromatin constituted approximately 43% in the nuclei of malignant melanoma elements from 22 female patients and ranged from 26 to 74%. The increased DNA levels and the decreased sex chromatin levels in tumor cell nuclei seem to indicate anaplasia and deep gene level alterations occurring in the malignant cell.



- 0547 PROTOPLASMIC INCLUSIONS IN MALIGNANT EPITHELIAL TUMORS. (Ger.) Kertikowa, S. (Med. Inst. Warna, Bulgaria). *Zbl Allg Path* 114(3):338-343, 1971.

Intracellular protoplasmic inclusions were found in 16 of 115 tumor specimens (80 biopsies and 35 necropsies). Of these, 11 were undifferentiated fast-growing tumors located at different sites. The inclusions had a star-like, oval or ring-like shape and varied between 5-30  $\mu\text{m}$  in size. They were seen mainly in cells located near necrotic foci and appeared to be separated from the cytoplasmic bulk by 4-10  $\mu\text{m}$ -wide clear strips. These inclusions appear to result from the altered metabolism of the tumor cell.

- 0548 LYMPHOTOXIN PRODUCTION IN HUMAN NEOPLASIA. (E.) Savel, H. (U. Vermont Coll. Med., Burlington) and T. Moehring. *Proc Soc Exp Biol Med* 137(2):374-376, 1971.

Peripheral blood lymphocytes were obtained from noncancer patients, from patients with Hodgkin's disease, and from patients with malignant conditions other than Hodgkin's disease; lymphocytes were established in culture and the ability of lymphocytes from Hodgkin's disease patients to form lymphotoxin in response to phytohemagglutinin was observed. Lymphotoxin production was measured by the uptake of  $^{14}\text{C}$  amino acids by mouse fibroblasts following the addition of supernatants from human lymphocytes previously exposed to phytohemagglutinin. Lymphocytes from noncancer patients and from patients with cancer other than Hodgkin's disease released lymphotoxin in response to phytohemagglutinin; lymphocytes from Hodgkin's disease patients showed a marked decrease in lymphotoxin formation. When lymphotoxin production was studied in lymphocytes from the 3 sources without the benefit of phytohemagglutinin stimulation, it was found that lymphocytes from Hodgkin's disease patients produced lymphotoxin whereas lymphocytes from noncancer patients and from patients with cancer other than Hodgkin's disease did not.

- 0549 MICROKINEMATOGRAPHIC AND ELECTRON MICROSCOPIC STUDIES OF CELL SURFACES, AND CONTACT CELLS OF A HUMAN CARCINOMA HEP2 CELL LINE. (Ger.) Strauli, P. (Zurich U., Switzerland), R. Lindenmann and G. Haemmerli. *Virchow Arch Path Anat* 8(2):143-161, 1971.

Ultrastructural cell surface investigations of a HEP2 cell line derived from a lymph node metastasis of a human larynx carcinoma and maintained in monolayer culture were carried out on trypsin-digested material. In addition, HEP2 cells were inoculated into golden hamsters and gave rise to solid tumors. Electron microscopy did not reveal qualitative differences between the structure of cells grown *in vitro* and *in vivo*. The spherical tumor cells displayed large numbers of bud-like formations on their surface immediately after explantation. Microkinematography allowed the distinction between passive and active bud-like

formations. The term of "microvilli" was substituted by the term of "microspikes" for the active short-life buds which were substituted by elongated formations when cell flattening occurred. The passive buds of the mitotic cells were considered to be retraction fibrils. Intermediate functions were observed on the surface of *in vivo*-grown cells where no cell flattening occurred. Desmosome formation could not be ascertained in the monolayer culture because of the trypsin treatment; however, formations referred to as semidesmosomes were seen and attributed to the effect of trypsin on the desmosomic bridges. Intensive mitotic activity could be observed during the development of this cell surface contact system. The results are considered to constitute a preliminary step in the elucidation of the intercellular contact mechanisms.

- 0550 NUCLEOSIDE TRANSPORT BY NOVIKOFF RAT HEPATOMA CELLS GROWING IN SUSPENSION CULTURE: SPECIFICITY AND MECHANISM OF TRANSPORT REACTIONS AND RELATIONSHIP TO NUCLEOSIDE INCORPORATION INTO NUCLEIC ACIDS. (E.) Plagemann, P. G. (Med. Sch., U. Minnesota, Minneapolis). *Biochim Biophys Acta* 233(3):688-701, 1971.

Kinetic analyses of the transport of nucleosides including guanine, inosine, uridine and cytidine by Novikoff rat hepatoma cells were carried out using ascending paper chromatography; kinetic constants ( $K_m$ ,  $v_{max}$  and  $K_m/K_i$  ratio) for the transport of the nucleosides by tumor cells were determined. Transport of adenosine, guanosine, inosine, uridine and cytosine was inhibited in a simple competitive manner by heterologous purine or pyrimidine ribonucleosides, thymidine, persantin and phenethyl alcohol. The apparent  $K_m$  values were similar for the transport of the nucleosides, ranging from about 8  $\mu\text{M}$  for adenosine transport to 23  $\mu\text{M}$  for cytidine transport. The  $K_m/K_i$  ratios for the inhibition of guanosine transport by inosine and of inosine transport by guanosine were both close to 1, suggesting that these 2 nucleosides were transported by a single system. It was thought that adenosine was not transported by the guanosine-inosine transport system. The  $K_m/K_i$  ratio for inhibition of uridine transport by cytidine and of cytidine transport by uridine was close to 1; however, the  $K_m$  and  $v_{max}$  values for cytidine and uridine and uridine transport were consistently different. Nevertheless, it was thought that uridine and cytidine were transported by a single system. All transport systems were similarly inactivated by treatment of hepatoma cells by *p*-chloromercuribenzoate. Uridine transport was evidently inhibited by heating cells to 47.5° for 5 min. as well as by treating cells with *p*-chloromercuribenzoate. Energy metabolism inhibitors, including NaCN, iodoacetate and 2,4-dinitrophenol inhibited the uridine transport system at high concentrations only. Competitive inhibition of nucleoside transport by heterologous nucleosides, persantin or phenethyl alcohol resulted in a competitive inhibition of nucleoside incorporation into nucleic acids in cells;

this suggested that the transport into hepatoma cells of nucleosides is the rate-limiting factor in the incorporation of nucleosides into nucleic acids.

- 0551  $\alpha_1$ -FOETOPROTEIN AND CHILDREN'S CANCER. (E.) Mawas, C. (Inst. Sci. Res. Cancer, Villejuif, France), D. Buffe, O. Schweisguth and P. Burtin. *Rev Europ Etud Clin Biol* 16:430-435, 1971.

Sera from a total of 188 children with various malignant conditions were tested for the presence of  $\alpha_1$ -fetoprotein. Of 139 sera from patients with nephroblastoma, symphoma, osteosarcoma, lymphoma, embryonal sarcoma, brain tumors and other conditions, none showed  $\alpha_1$ -fetoprotein. Of 23 serum samples from children with hepatoma, 21 were positive for  $\alpha_1$ -fetoprotein and of 27 serum samples from children with malignant teratoma, 15 were positive for  $\alpha_1$ -fetoprotein. Teratoma patients included patients with tumors of the ovaries, mediastinum, and testicles. Twelve serum samples from hepatoma and teratoma patients were negative for  $\alpha_1$ -fetoprotein; 11 of these negative sera came from patients who were tumor-free following treatment and from patients with regressed tumors.

- 0552 ELECTROGENESIS IN MOUSE NEUROBLASTOMA CELLS *IN VITRO*. (E.) Nelson, P. G. (Nat'l. Inst. Child Hlth., Nat'l. Inst. Hlth., Bethesda, Md.), J. H. Peacock, T. Amano and J. Minna. *J Cell Physiol* 77(3):337-352, 1971.

Subcutaneous neuroblastomas from male A/J mice were excised, minced and prepared for cell culture; an uncloned cell line and a cloned line were established and used in electrophysiologic investigations. Cloned cells were studied 8-10 months after initial dissociation from the primary neuroblastoma, the other cells were studied 3-5 wk after dissociation. Electrophysiologic measurement of neuroblastoma cell membrane properties were made by passing current pulses across the cell membrane from an intracellular microelectrode. The mean membrane resting potential of uncloned cells was 27.7 mv, while the mean membrane resting potential of cloned cells was 37.5 mv. Passive membrane electrical properties of neuroblastoma cells were similar to properties of sympathetic neurons in intact preparations. Depolarizing pulses of electricity elicited action potentials in neuroblastoma cells. The size of the action potential depended on the resting membrane potential. Cloned neuroblastoma cells responded to stimulation with action potentials in 79% of cases, while action potentials were elicited in 94% of uncloned cells. The incidence of repetitive firing was higher in uncloned cells plated 10-14 days before electrical stimulation than in uncloned cells plated 7 days before stimulation. In addition, the incidence of repetitive firing was higher in uncloned cells (23% of cells showing repetitive firing) than in cloned cells (2% of cells showing repetitive firing). Treating neuroblastoma cells with tetrodotoxin blocked spike generation in stimulated cells.

- 0553 SOME ASPECTS OF THE ROLE OF VITAMIN B<sub>12</sub> AND FOLIC ACID IN DNA-THYMIDINE SYNTHESIS IN A NEOPLASTIC C3H MOUSE CELL STRAIN. (E.) Rotherham, J. (Nat'l. Cancer Inst., Bethesda, Md.), F. M. Price, T. T. Otani and V. J. Evans. *J Nat Cancer Inst* 47(2):277-287, 1971.

Neoplastic C3H mouse cells were grown in media containing folic acid ( $0.57 \times 10^{-6}$  M), vitamin B<sub>12</sub>, adenine, and either thymidine or deoxyuridine; DNA synthesis in these cells, and changes in DNA synthesis produced by alterations in the growth medium, were observed. Cells in media consisting of folate + B<sub>12</sub> + adenine synthesized similar amounts of DNA when deoxyuridine was substituted for thymidine. In cells grown in media consisting of folate + adenine but no B<sub>12</sub>, the amount of DNA formed was less when deoxyuridine was substituted for thymidine. Without B<sub>12</sub> DNA synthesis in the presence of deoxyuridine was less than in the presence of thymidine. When the folate molarity was decreased in the adenine- and B<sub>12</sub>-containing media, DNA synthesis with deoxyuridine was again reduced. Omission of adenine from the basic medium resulted in a decrease in DNA synthesis when deoxyuridine was substituted for thymidine. The effect of B<sub>12</sub> on DNA synthesis and the incorporation of <sup>14</sup>C-formate was also studied. In medium containing deoxyuridine and deoxycytidine, but not in medium containing thymidine, the amount of DNA synthesized was greater when B<sub>12</sub> was present than when it was absent. Cells grew well in media in which methyl-B<sub>12</sub> and deoxyuridine were used as precursors for DNA-thymidine synthesis. Methylcobalamin did not provide a pool of methyl groups for DNA-purine or DNA-thymidine synthesis. It was concluded that B<sub>12</sub> acted to increase DNA-thymidine synthesis in mouse cells by raising limiting levels of folate coenzymes.

- 0554 CHROMOSOMAL CHARACTERISTICS OF NEUROGENIC TUMOURS IN ADULTS. (E.) Mark, J. (Inst. Path., U. Lund, Lund, Sweden). *Hereditas* 68(1): 61-100, 1971.

Karyotype studies were performed on 50 cerebral and 1 cerebellar astrocytic gliomas, 1 oligodendroblastoma and 1 medulloblastoma. Seventy-four percent of gliomas had chromosome stemlines in the diploid region; there were 9 tetraploid and 4 triploid stemline tumors. Seventy-six percent of tumor stemlines showed 1 or more marker chromosomes. In the hypodiploid stemline tumors, numerical deviations in chromosomes were concentrated in the D and C groups. All the pseudodiploid gliomas had numerical deviations in the C group of chromosomes. The C chromosomes were also the predominant site of deviations in hyperdiploid gliomas; the D group was not as often involved in numerical deviations in hyperdiploid gliomas as in hypo- and pseudodiploid gliomas. Marker chromosomes were found in 14 of 16 hyperdiploid tumors. Loss of D group chromosomes was a consistent finding in all the gliomas. Thirteen gliomas showed double-minute chromosomes; in 4 gliomas, double-minutes were found in all or most cells. Pseudodiploid stemlines were seen most often in younger patients (35-45-yr-old). Female patients with hypodiploid tumors were usually younger than female patients



with hyperdiploid tumors. Almost 2/3 of the hyperdiploid tumors were found in males, and 3 of the 4 triploid tumors were found in males. There appeared to be an association between occurrence of hyperdiploidism, a long duration of symptoms prior to operation, and parietally located tumors.

- 0555 CORRELATION OF NUCLEOLINI WITH FINE STRUCTURAL NUCLEOLAR CONSTITUENTS OF CULTURED NORMAL AND NEOPLASTIC CELLS. (E.) Love, R. (Dept. Path., Jefferson Med. Coll., Philadelphia, Pa.) and R. Z. Soriano. *Cancer Res* 31(7):1030-1037, 1971.

The nucleoli of cells in stationary and exponentially growing cultures of human female embryo cells (diploid) and in cultures of HeLa cells (aneuploid) were examined by light and electron microscopy. Under the light microscope, 61% of exponentially-growing diploid cell nucleoli were found to contain nucleolini in numbers too large to count; nucleolini in these cells were similar in size. Under the light microscope, 61% of cells in cultures of stationary diploid cells contained fewer than 5 nucleolini per nucleolus; nucleolini in these cells were of various sizes. Nucleolar ribonucleoprotein of a kind which was not contained in nucleolini was abundant in stationary, and scanty in growing, diploid cells. The nucleolini in the light microscope correspond to the light fibrillar centers with, or without a peripheral dense fibrillar component in electron micrographs. The remainder of the nucleolus surrounding the nucleolini corresponds to the granular component in the electron micrograph. In exponentially growing diploid cells with abundant nucleolini the dense fibrillar material predominated in the form of incomplete spherical structures enclosing some light fibrillar material. In stationary diploid cultures with few large nucleolini there were few large light fibrillar centers and the granular component of the nucleolus was abundant. In day old HeLa cultures the nucleolini were numerous, relatively small and somewhat uneven in size. Light fibrillar centers with peripheral dense fibrillar material were morphologically similar to nucleolini in electron micrographs. In 4 day-old HeLa cells nucleolini and fibrillar centers were fewer, larger and more uneven in size. Treatment of HeLa cells with 5 mM thymidine resulted in few huge nucleolini and very large light fibrillar centers with dense fibrillar peripheries.

- 0556 CYTOLOGY IN LYMPHOSARCOMA CELL LEUKEMIA. (E.) Schrek, R. (VA Hosp., Hines, Ill.) and W. J. Donnelly. *Amer J Clin Path* 55(6):646-654, 1971.

- 0557 GENETIC PREDICTABILITY IN BREAST CANCER RISK: SURGICAL IMPLICATIONS. (E.) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.) and A. J. Krush. *Arch Surg* 103(1):84-88, 1971.

- 0558 HAPTOGLOBIN (H<sub>p</sub>) LEVELS IN THE BLOOD SERUM OF PATIENTS SUFFERING FROM LEUKEMIA. (E.) Gurda, M. (Med. Acad., Cracow, Poland). *Acta Med Pol* 11(4):383-386, 1970.

- 0559 PROTEIN FRACTIONS, THEIR AMINO ACID COMPOSITION AND FREE AMINO ACID LEVELS OF HUMAN UTERINE TUMORS. (Rus.) Misheneva, V. S. (N. N. Petrov Sci. Res. Inst. Oncol. Leningrad, U.S.S.R.). *Vop Onkol* 17(5):19-24, 1971.

- 0560 MUSCLE AND TUMOR TISSUE CHOLINESTERASE ACTIVITY DURING THE GROWTH OF JENSEN'S SARCOMA. (Rus.) Luk'yanets, V. V. (Dnepropetrovsk Med. Inst., U.S.S.R.) and Yu. P. Artamonov. *Vop Onkol* 17(4):78-80, 1971.

- 0561 BIOCHEMICAL AND CYTOLOGICAL STUDIES OF LEUKOCYTES IN CHLOROLEUKEMIA. (Rus.) Luganova, I. S. (Sci. Res. Inst. Hematol. Blood Transf., Leningrad, U.S.S.R.) L. M. Rozanova, M. F. Kharchenko, V. N. Filippova, V. B. Letskiy, and I. F. Seytes. *Probl Gemat* 16(5):L20-23, 1971.

- 0562 CHROMOSOMAL PATTERNS OF PATIENTS WITH LEUKEMIA, ERYTHREMIA OR MYELOIC FIBROSIS. (Rus.) Zakharova, A. V. (Central Inst. Hematol. Blood Transf., Moscow, U.S.S.R.) M. I. Korenevskaya, R. A. Mokeyeva, N. F. Klimova, L. G. Kovalova, Ye. I. Bartashchuk, E. I. Terent'yeva. *Probl Gemat* 16(5):3-8, 1971.

- 0563 CYTIDINE-5<sup>1</sup>-MONOPHOSPHATE-N-ACETYLNEURAMINATE SYNTHETASE IN NORMAL AND LEUKEMIC HUMAN LEUKOCYTES. (Ger.) Kügelgen, B. (Inst. Pharmacol., U. Köln, Germany) and W. Gielen. *Klin Wschr* 49(12):710-711, 1971.

- 0564 CHROMOSOMAL REPLICATION IN CHRONIC MYELOCYTIC LEUKEMIA CELLS. (Ger.) Büchner, T. (Wilhelms U., Westfalen, Germany) and B. Gattermann. *Klin Wschr* 49(11):644-648, 1971.

- 0565 CHROMOSOMAL CHANGES DEVELOPED IN A MALIGNANT MELANOMA. (Fr.) Berger, R. (Inst. Genet., Paris, France), J. Lejeune and J. Lacour. *Rev Europ Etud Clin Biol* 16:476-481, 1971.

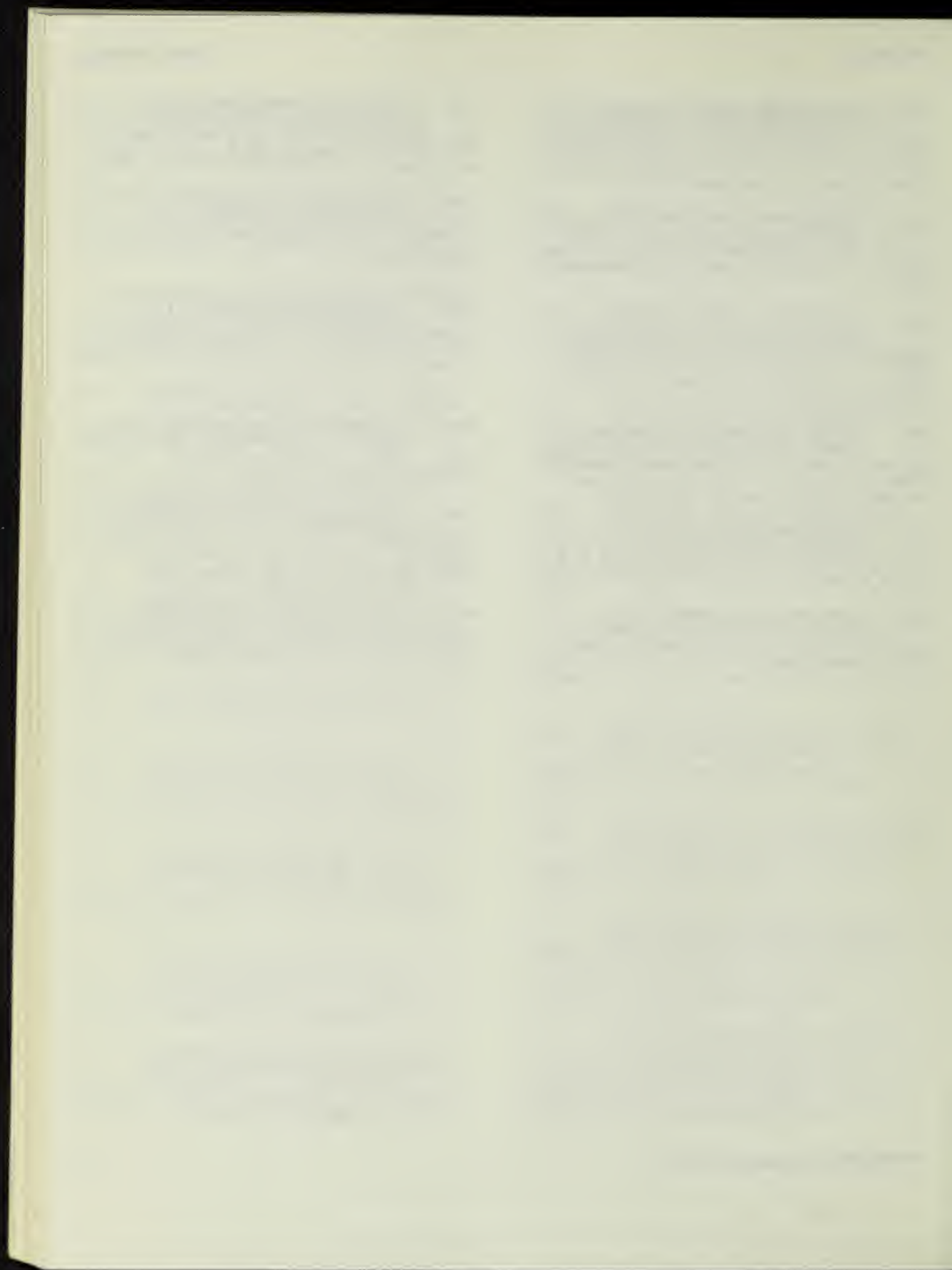
- 0566 FIBRINOLYTIC ACTIVITY IN MALIGNANT NEOPLASTIC DISEASES. (E.) Omar, J. B. (G. S. V. M. Med. Coll., Kanpur, India), H. Saxena, H. S. Mital, V. K. Rohatgi and M. G. Gopal. *J Ass Physicians India* 19(4):293-296, 1971.

- 0567 AMINO ACID NAPHTHYLAMIDASE ISOZYMES IN CANCER CELLS AND NORMAL CELLS. (E.) Beckman, L. (Dept. Path., U. Umea, Sweden), E. Lundgren and P. A. Rydelius. *Clin Genet* 2(1):37-40, 1971.

- 0568 CLONAL PATTERN OF METASTASIS IN A CASE OF MALIGNANT MUCOEPIDERMOID TUMOUR OF THE PALATAL SALIVARY GLAND. (E.) Saksela, E. (Helsinki U. Central Hosp., Finland), B. Grahne and U. Surala. *Acta Otolaryng* 71(5):430-434, 1971.
- 0569 THE ULTRASTRUCTURE OF CARCINOMAS DEVELOPED ON THE LIMBUS. (Hun.) Radnot, M. (U. Budapest, Hungary) and K. Lapis. *Szemeszet* 107(2):82-95, 1971.
- 0570 PROLIFERATION OF YOSHIDA ASCITES TUMOR CELLS IN SUSPENSION CULTURE: THE ROLE OF GLUCOSE. (Ger.) Averdunk, R. (Inst. Clin. Chem., Free U. Berlin, Germany) and E. Liss. *Z Naturforsch* 26(6):595-598, 1971.
- 0571 CARCINOMA OF THE UTERINE CERVIX: ZINC LEVELS IN GRANULOCYTES. (Ger.) Weise, W. (Reg. Clin. Gynecol., Magdeburg, Germany), D. Wolansky and G. Agatha. *Radiobiol Radiother* 12(1):71-77, 1971.
- 0572 SULFHYDRYL GROUP LEVELS IN SERUM PROTEIN FRACTIONS OF TUMOR BEARING ANIMALS. (Rus.) Shvedova, V. N. (Inst.-Chem. Pharm., Leningrad, U.S.S.R.) and Yu. S. Zavadskaya. *Vop Onkol* 17(5):48-51, 1971.
- 0573 PROLACTIN CELL ADENOMAS OF THE PITUITARY: STRUCTURAL AND ULTRASTRUCTURAL STUDIES, ANATOMICAL AND CLINICAL CORRELATIONS. (Fr.) Racadot, J. (Pitie-Salpetriere Med. Sch., Paris, France), E. Vila-Porcile, F. Peillon and L. Oliver. *Ann Endocr* 32(2):298-305, 1971.
- 0574 IMMATURE CELL MONOCYTIC LEUKEMIAS. (Ger.) Schmalzl, F. (Innsbruck U. Clin., Austria) *Blut* 22(4):157-174, 1971.
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# **CARCINOGENESIS ABSTRACTS**

**National Cancer Institute**

**U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • National Institutes of Health**





## CARCINOGENESIS ABSTRACTS

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**Editor**

Robert Love, M.D.  
Jefferson Medical College, Philadelphia

**Associate Editor**

George P. Studzinski, M.D.  
Jefferson Medical College, Philadelphia

**NCI Staff Consultants**

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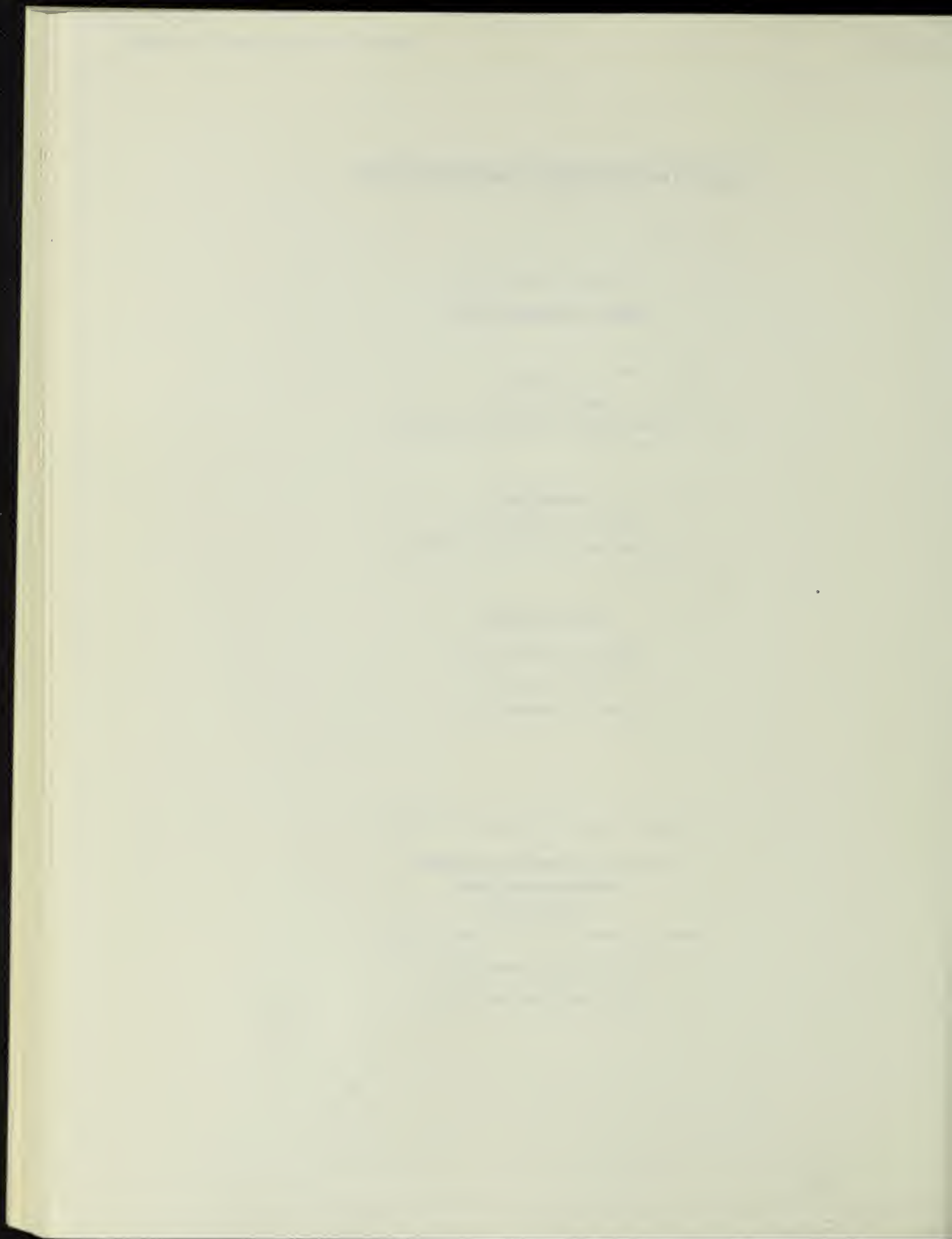
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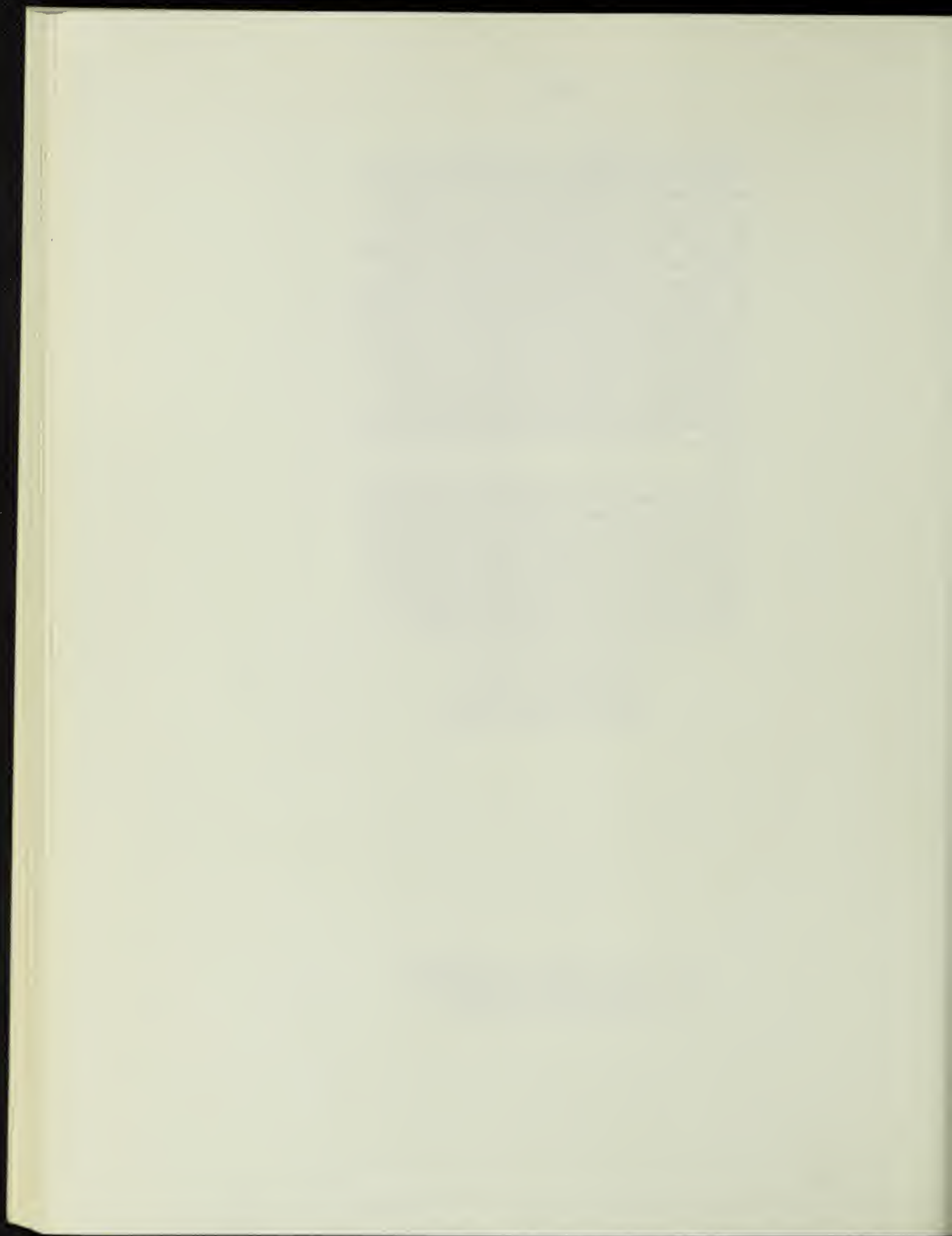
## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain two-hundred abstracts and twenty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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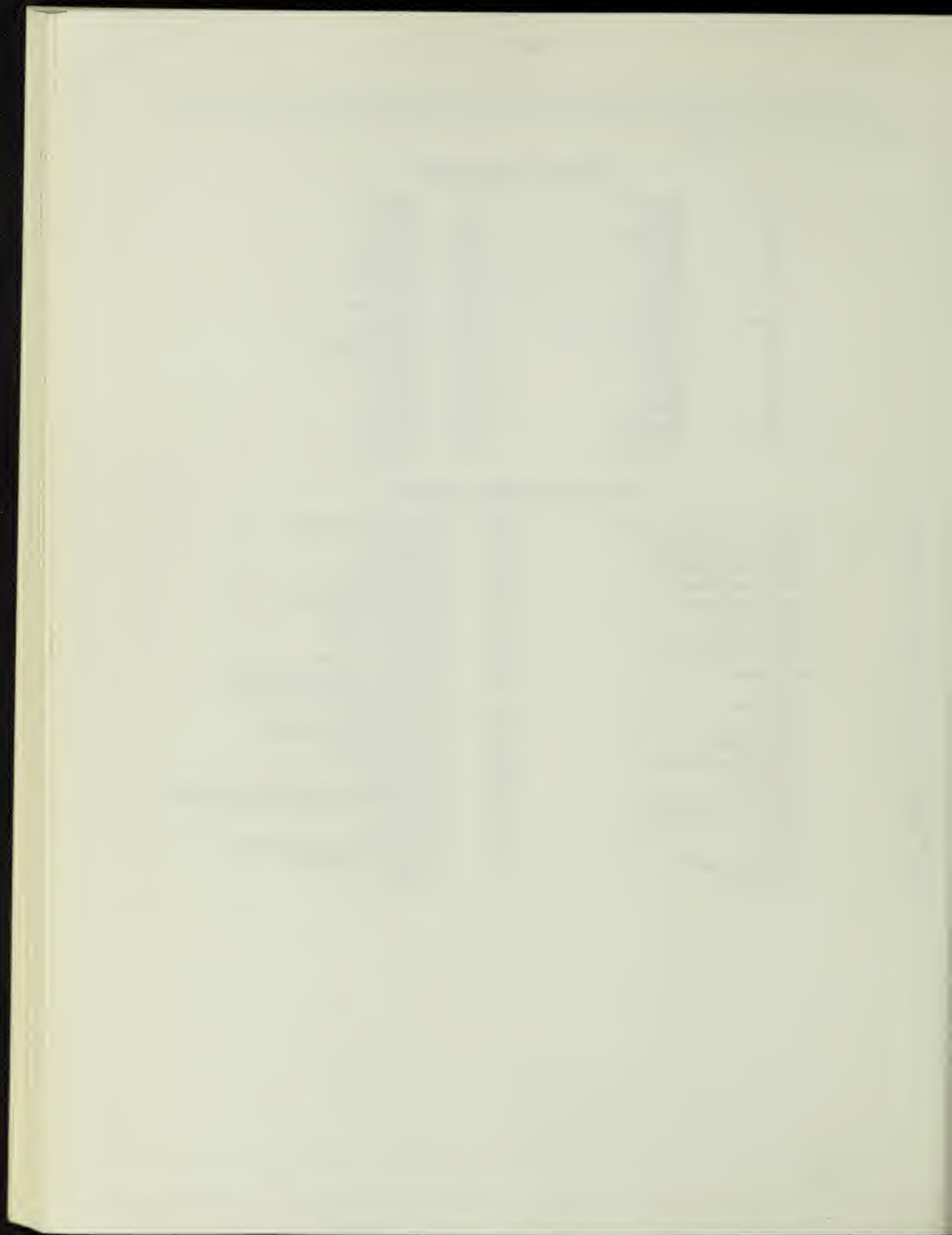
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## LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

## ABBREVIATIONS USED IN ABSTRACTS

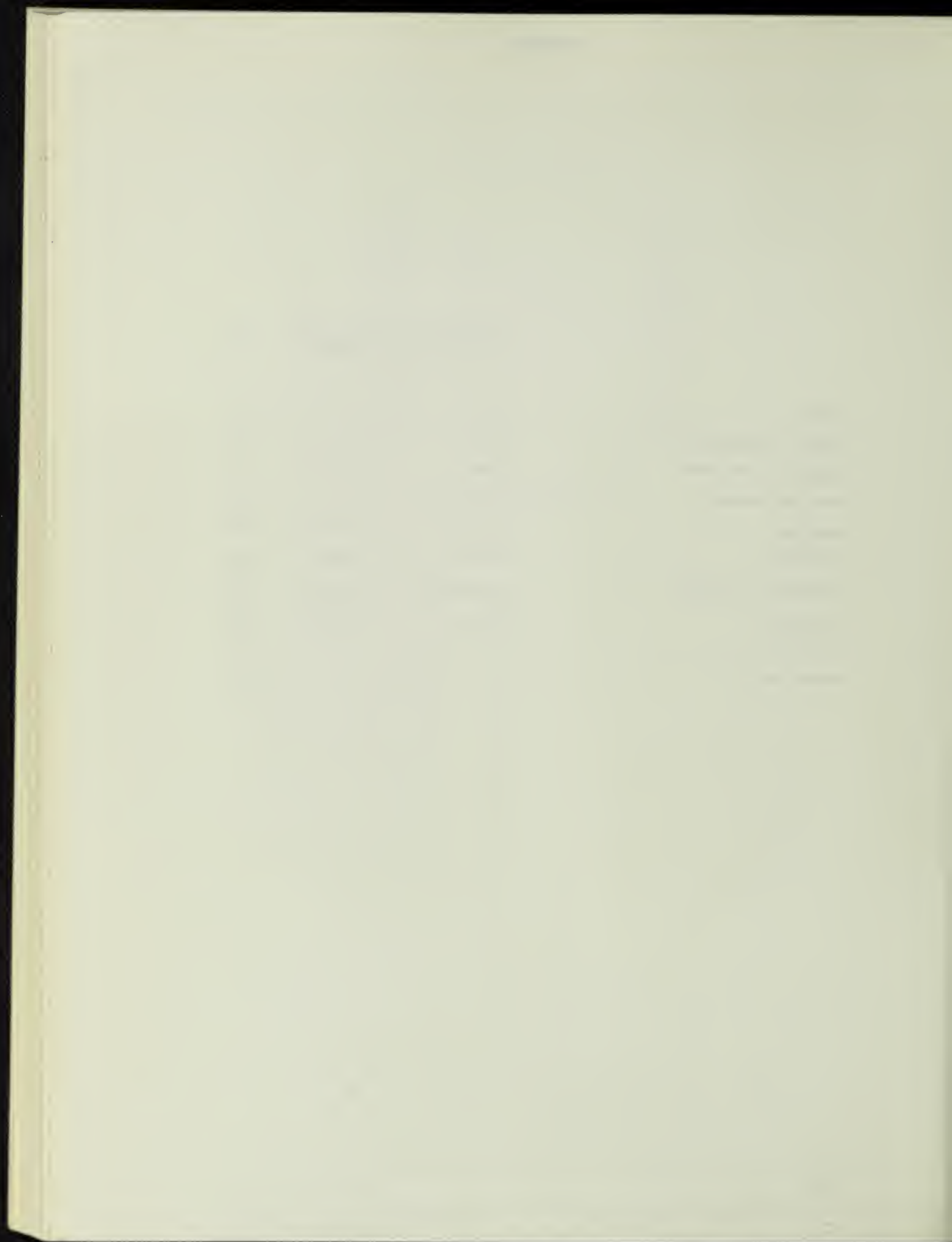
ACTH	adrenocorticotrophic hormone	mC, $\mu$ C	milli-, microcurie(s)
ADP	adenosine diphosphate	mg	milligram(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
BSP	sulfobromophthalein	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram ( $10^{-9}$ )
CNS	central nervous system	pg	picogram ( $10^{-12}$ )
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
$\mu$ g	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	SGOT	serum glutamic-oxalacetic transaminase
kg	kilogram(s)	SGPT	serum glutamic-pyruvic transaminase
LD <sub>50</sub>	median lethal dose(s)	U	unit(s)
LDH	lactic acid dehydrogenase	UV	ultraviolet
m	meter(s)	WBC	white blood cells (leukocytes), white blood count
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
$\mu$ M	micromolar		





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# REVIEW

- 0601 IMMUNOLOGIC ASPECTS OF NEOPLASIA. (E.) Mathe, G. (No affiliation). *S Afr Cancer Bull* 15(2):58-67, 1971.

The current status of research into the immunological aspects of cancer is reviewed and recent findings, including findings reported at the Tenth International Cancer Congress, are discussed. Most investigators agree that both cellular and humoral immunity play important roles in the immune response to tumors. Cellular immune responses (via lymphocytes) are perhaps of greatest importance in killing tumor cells. *In vitro* studies have suggested that tumor cells are foreign as compared with the host's normal tissues. This foreignness, which is caused by tumor-specific "transplantation" antigens, evokes an immune response to the tumor; the response can be detected by membrane immunofluorescence tests. Colony-inhibition tests have shown that globulin-containing serum and immunity cells can inhibit the growth of malignant autochthonous cells. In one study, increased DNA synthesis was seen in lymphocytes after contact with autochthonous malignant cells but not after contact with non-malignant cells. Possibly the patient with cancer represents a situation in which the immunological control system has failed or has been outflanked. In another report, the high incidence of cancer among patients with immunological deficiency diseases was noted. Further evidence for an association between immunologic inadequacy and oncogenesis includes the findings that all tested carcinogens are immunosuppressants, and that, phylogenetically, the appearance of neoplasia and radiosensitive lymphoid cells parallels the development of an immunological system. Despite intensive investigation, the exact relationship of altered host defense mechanisms to the etiology and pathogenesis of human malignant disease is still obscure. In a study of the immune response of patients to a strong protein, abnormal results were found in patients with lymphoproliferative disorders contrasted with results in patients with solid tumors and in normal controls. In a related study, the immune response in solid tumor patients who had no evident disease after operation was slightly greater than that in normals, while the immune response in patients with metastatic solid tumors was slightly lower than that in normals. Evidently, immune deficiency develops as malignant disease progresses, and does not develop before the development of malignancy. Tumor antigens were reported as being associated with a variety of tumors, including tumors of the digestive system, neuroblastomas and sarcomas. (No references)

- 0602 THE ANTIGENIC STRUCTURE OF HUMAN AND ANIMAL TUMOR CELLS. (Pol.) Harlozinska, J. (Polish Acad. Sci., Wroclaw). *Postepy Hig Med Dosw* 25:367-389, 1971.

The antigenic structure and the methods available for the study of the immunological phenomena related to neoplastic growth (both spontaneous growth

and induced growth) are reviewed. Information available so far shows that the antigenic structure of the neoplastic cell differs both qualitatively and quantitatively from that of the corresponding normal tissue cell. The variety of antigens present within a neoplastic cell is determined mainly by the tumor inducing agent. The neoplastic tissue may acquire new antigens or lose some antigens specific for normal tissue. Specific antigens are located on the surface of the neoplastic cell. The achievements reached in this field open new methods for investigating tumor etiology and for classifying oncogenic viruses. (168 references)

- 0603 EFFECTS OF TUMOR VIRUSES ON CELLULAR GROWTH AND TRANSFORMATION. (E.) Smith, T. R. (U. Minnesota Med. Sch., Minneapolis) and H. H. Zinneman. *Nebraska Med J* 56(9):367-374, 1971.

The role of viruses in affecting the cellular growth of infected cells, and aspects of the transformation of cells by viruses, are reviewed. Primary characteristics of the transformation process in virally infected cells include: increased growth rate of cells; lack of contact inhibition of cell growth and lack of anchorage dependency in cultures, resulting in the production of multilayered clones of cells; occurrence of random chromosomal abnormalities; production of tumors upon inoculation of tumor viruses; the appearance of new antigens in transformed cells; change in nutrient requirements in transformed cells *in vitro*; transformation of cells in the "S" phase of mitosis. DNA viruses establish a permanent association with the cells they transform; they integrate the DNA structure of the virus into the cellular DNA. RNA viruses do not exhibit any evidence of a permanent relationship with cellular components. Cellular events of DNA viruses depend on the host cell. In permissive cells, viruses multiply, but in nonpermissive cells viruses transform the cell without multiplying. The primary change in the DNA virus-transformed cell is the production of a surface or transplantation antigen ("tumor-specific transplantation antigen"). Among RNA viruses, it has been found that the antigenicity of Rous sarcoma virus (RSV) is determined strictly by the strain of the RSV "helper" virus used in the production of RSV from "nonproducer" cells. The original idea that RSV was "defective" is now known to be incorrect. The role of the helper virus is really that of extending the limited host range of RSV; the helper virus adds its determinants to the outer structure of the RSV particle. RSV viruses have recently been found to produce tumors in animals. Not only is viral nucleic acid necessary for infection of cells but some immunologic changes in the host must occur before infection and transformation can take place. Evidence for a relationship between viruses and human cancer includes the finding of virus-like particles in cells and plasma of leukemic patients (although these particles may have been only "passenger viruses"), and the presence of Epstein-Barr virus in Burkitt's lymphoma cells. Human cervical and mammary carcinoma may also have some etiologic relationship to viruses. (32 references)

- 0604 THE BREAST AND THE PILL. (E.) Lesnick, G. J. (Mount Sinai Sch. Med., New York, N.Y.). *New York J Med* 71(17):2058-2060, 1971.

The possibility of a connection between use of oral contraceptives and mammary carcinoma is discussed. Although oral contraceptive use is associated with functional and structural changes in mammary tissue, there have been no reports in which malignant neoplasms were attributable to the use of oral contraceptives. However, rapid growth of mammary fibroadenomas has been observed in users of oral contraceptives. In spite of the negative evidence for a causal connection between oral contraceptives and breast cancer, concern has been expressed about potential hazards of long-term oral contraceptive use. This concern is stimulated by what is known of the effects of estrogens on breast cancer. Estrogens can stimulate the occurrence of breast cancer in several species of animal, and administered estrogen will often cause exacerbation of metastatic breast cancer if given to women less than 5 yr after menopause. However, evidence against a role for estrogens in mammary carcinogenesis is provided by the observation that there is no decrease in the breast cancer prevalence rate among post-menopausal women. Furthermore, despite the consumption of large amounts of estrogens by millions of women over the past 30 yr as treatment for menopausal symptoms or for osteoporosis, there is no evidence that persons so treated show a higher incidence of breast cancer. Progesterones -- another class of components of oral contraceptives -- have not been noted to be carcinogenic in either man or animals. (17 references)

- 0605 EMBRYONAL NEOPLASM OF THE BLASTEME. (Fr.) Payan, H. (Fac. Med., Marseilles, France). *Anat Path* 19(2):153-165, 1971.

The common features of the embryonal tumors are determined by their histogenesis. Their development from blastemic laminae appears to be accompanied by the formation of constitutive elements which are common, to a certain extent, between pulmonary blastoma, neuroblastoma and Wilms' tumor. The individual features of these tumors are determined by their regional character of differentiation which is induced by the original blastema. It can be assumed that an organizational induction occurs at a certain moment which may be associated either with a chemical entity or with intertissue surface effects, and promotes the proliferative process. The dedifferentiated tissue of the blastema may, sometimes, be endowed with multiple potentialities producing epithelial and connective structures which occur in Wilms' tumor. In other cases a single blastemic lamina develops generating embryonal sarcoma. Hepatoblastoma and tumors of the pulmonary blastema imply the coexistence of 2 distinct cell laminae which generate the epithelial and connective structures occurring in these neoplasms. Inclusions from surrounding tissues, metaplastic processes and the presence of striated muscle in nephroblastoma, hepatoblas-

toma and pulmonary blastemic tumors constitute characteristic heteroplastic features of these neoplasms. The embryonal origin of blastemic tumors is easier to observe in children than in adults. A sudden outburst of quiescent elements or a phenomenon of regressive metaplasia from an adult tissue undergoing a dedifferentiation process responsible for oncogenic proliferation are among the pathogenetic mechanisms assumed in the latter case. Ultrastructural studies and further research dedicated to interactions between teratogenesis and oncogenesis should throw more light on the pathogenesis of the blastemic tumors. (63 references)

- 0606 IMMUNOLOGICAL PHENOMENA AND CARCINOGENESIS. (Pol.) Srebo, Z. (Acad. Med. Sci., Krakow, Poland). *Postepy Hig Med Dosw* 25:391-414, 1971.

Current views on the role of immunological mechanisms in preventing or promoting the development of experimental or spontaneous tumors are discussed. Tumor transplant and tumor transplant specific antigens as well as their specific features are reviewed. Reference is made to virus-induced tumor antigens whose features are determined by the viral rather than by the transformed cell genome. The antigenic features of chemically induced tumors are discussed. The assumption that chemical carcinogens produce the activation of preexistent latent oncogenic viruses is analysed; virus specific antigens had been detected in chemically-induced tumors. The effects of tissue transplant and tumor transplant antigens as well as carcinoembryonal antigens are reviewed. The role of the immunological condition of the organism during the carcinogenic process as well as certain aspects of spontaneous tumor regression are discussed. New developments in cancer immunotherapy are expected. (154 references)

- 0607 GENETIC CHANGES IN CANCER: CAUSE OR EFFECT? (E.) Nowell, P. C. (U. Pennsylvania Sch. Med., Philadelphia). *Hum Path* 2(3):347-348, 1971.

Current views of the genetic changes associated with neoplastic change are briefly reviewed. Irreversible genetic changes apparently occur in almost all mammalian tumors before the tumors reach macroscopic size. At the cellular level there is much evidence that changes in genetic structure and function are present in most cancers; whether these changes are involved in the initiation of the neoplastic process, or whether they are secondary phenomena resulting from that process, remains a debated question. Evidence for alterations in the genome of cancer cells comes from the observation of inappropriate hormones and fetal antigens produced by human tumors, as well as from the observation that disorders resulting in human chromosomal breakage (e.g. Bloom's syndrome) are associated with an increased incidence of neoplasia. The nature and variety of postulated initial



genetic changes remain obscure; this initial change may be a classical somatic mutation or may be associated with virus infection. The recent demonstration of RNA-dependent DNA polymerase in several neoplasms has led to the suggestion of mechanisms by which oncogenic RNA viruses, as well as DNA viruses, could intimately interact with the cell's genetic apparatus. While increasing evidence points towards one or another of these various genetic mechanisms in the initiation of different human cancers, it seems unlikely that the same process will be found to be operative in every instance. Studies on human populations indicate that the cell's genetic activity is ordinarily profoundly altered in the development of the neoplasm. Different pathways to this endpoint may exist in the initiation of different tumors. (No references)

0608 CURRENT RESEARCH REVIEW: TUMOR-SPECIFIC CELLULAR IMMUNITY. (E.) Cohen, A. M. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), J. F. Burdick and A. S. Ketcham. *J Surg Res* 11:421-431, 1971.

Techniques developed to demonstrate host cellular immunity to tumor allografts and applied to the study of tumor specific transplantation antigens (TSTA's) were reviewed. Early demonstration of cellular immunity against animal TSTA's was carried out in adoptive transfer experiments in which, e.g., the ability to reject skin and tumor allografts was passively transferred by i.v. injection of viable leukocytes from sensitized donors. Adoptive transfer of immunity to TSTA's has also been effected using i.p. injection of sensitized spleen or lymph node cells. In the neutralization technique (or "mixed leukocyte-tumor cell-technique") leukocytes are mixed *in vitro* and then injected into an immunosuppressed host; it can be shown that leukocytes from a specifically immunized host prevent or retard tumor growth. In delayed cutaneous hypersensitivity tests with guinea pigs, animals are immunized against allogeneic tissue by skin grafting, and spleen cells from donor animals are injected into sensitized guinea pigs, evoking a delayed cutaneous hypersensitivity reaction. Inhibition of macrophage migration has been shown to be an *in vitro* correlate of delayed cutaneous hypersensitivity. Inhibition of normal macrophage migration is effected by a soluble factor released from immune lymphocytes after specific antigenic stimulation. In lymphocyte transformation studies, the addition of specific antigen to a lymphocyte suspension results in the transformation of previously sensitized lymphocytes into large pyroninophilic blast cells which undergo mitosis. In cell mediated cytotoxicity tests, leukocytes are added to target cells and the number of target cells remaining after incubation is determined. Neutralization experiments, delayed cutaneous hypersensitivity tests, macrophage migration inhibition, lymphocyte transformation and cell-mediated cytotoxicity have been applied to the study of cell-mediated responses in human tumor-host systems. Human tumors which may have TSTA's as indicated

by these tests include: Burkitt's lymphoma, Hodgkin's disease, neuroblastoma and breast cancer. (79 references)

0609 SYNTHESIS AND METABOLISM OF DNA AND DNA PRECURSORS BY HUMAN NORMAL AND LEUKEMIC LEUKOCYTES: A SUMMARY OF RECENT INFORMATION. (E.) Gallo, R. C. (Natl. Cancer Inst., Bethesda, Md.). *Acta Haemat* 45:136-158, 1971.

The status of current knowledge concerning the metabolism and synthesis of DNA and some of the enzymes of DNA metabolism in normal and leukemic human leukocytes is reviewed. Precursor control mechanisms are discussed; although precursor control of DNA or RNA synthesis is increasingly viewed as a coarse rather than a fine control, it remains an important subject, since some of the most effective anti-tumor agents work at this level. The essential reactions of pyrimidine nucleoside biosynthesis and catabolism which have been verified in leukocytes are detailed. In human leukocytes, the mechanism of control of early enzymatic activities remains to be shown. Mechanisms for the immediate synthesis of the thymine nucleotide and of deoxyribosyl are of especial interest. An enzyme catalyzing conversion of ribonucleotides to deoxyribonucleotides has been demonstrated in human leukocytes. Technical problems and difficulties of data interpretation in a heterogeneous cellular system are discussed, and quantitative changes in enzyme systems during leukocyte maturation are described. Quantitative enzyme differences between normal and leukemic cells have been found (e.g., in alkaline phosphatase and pyrimidine deoxyribosyl transferase). Enzymes catalyzing replication and repair of DNA are of especial interest; little is known about these enzymes in human leukocytes. An enzyme analogous to viral RNA-dependent DNA polymerase has been found in human acute leukemic cells; the assay employed in the demonstration of this enzyme indicated that the enzyme did not occur in normal peripheral blood lymphocytes. It was stressed that in no case has a qualitative enzyme difference between normal and leukemic cells been demonstrated. (58 references)

0610 THE AGE DISTRIBUTION OF CANCER: IMPLICATIONS FOR MODELS OF CARCINOGENESIS. (E.) Doll, R. (U. Oxford, England). *J Roy Stat Soc* 134(2):133-166, 1971.

An examination is made of the relationship between the incidence of different types of cancer and age in different countries and the rate of change in incidence of cancer in test populations after exposure to cigarette smoke and other carcinogens for measured periods. The bearing of these studies on the perfection and application of mathematical models is discussed. Cancer registry data from various nations confirm the existence of 3 main patterns of cancer incidence at various ages: (1.) a peak incidence in childhood, adolescence, or early adult life followed by a decline or by a secondary rise in old

age; (2.) a rapid and regular increase in incidence from adolescence to 80-yr-old; (3.) a similar pattern in early life, diminishing in old age. A peak incidence of cancer at a given age is often attributable to previous exposure to a carcinogen on a single occasion or over a brief period (e.g., survivors of nuclear bomb explosions in Japanese cities in 1945). Statistical interest has centered on cancers which show a progressive increase in incidence with age; a simple power relationship between incidence and age has been used to describe cancer registry data. However, cancer incidence does not always vary in proportion to a power of age. It has been suggested that the difference between the age distribution of, e.g., lung cancers and other common epithelial cancers may be attributed to a progressive increase in the extent to which successive cohorts of men are exposed to agents responsible for the production of lung cancers, the degree of exposure to agents causing other types of cancer remaining stable. In studies of the differential incidence of bronchial cancer among cigarette smokers and nonsmokers, it was suggested that nonsmokers are exposed from birth to a weak agent capable of causing bronchial cancer. This possibility indicated that age at start of exposure to a potential carcinogen should be written into the power relationship equation of incidence and age. In studies of lung cancer in men, incidence rates among smokers rise approximately as a seventh power of age or as a fourth power of duration of smoking. Evidently, under conditions of prolonged and regular exposure to a carcinogen, the same mathematical model relating exposure to cancer incidence may hold in mice as well as in humans. In evaluating possible mechanisms of carcinogenesis in the light of mathematical models, no mechanism can be valid unless it leads to a relationship between cancer incidence and duration of exposure to carcinogen which approximates to a simple power relationship over a wide range of ages. Specific studies, in which cancer incidence among men was found to change when conditions of carcinogen exposure were modified in different ways, are reviewed. (28 references)

- 0611 GUT BACTERIA AND AETIOLOGY OF CANCER OF THE BREAST. (E.) Hill, M. J. (St. Mary's Hosp. Med. Sch., London, England), P. Goddard and R. E. O. Williams. *Lancet* 2(7722):472-473, 1971.

Geographical variations in the incidence of mammary carcinoma seem to be correlated with variations in the fat content of diets. A hypothesis relating diet, intestinal bacteria and mammary carcinoma is presented. The hypothesis requires that intestinal bacteria be able to produce from steroids associated with a high-fat diet a carcinogen that might act on mammary tissue or an estrogen that might stimulate tumor growth. The production by intestinal bacteria of estradiol, estrogen, and 17-methoxy-estradiol from androstenedione and from cholestenone and 3-oxo-chol-4en-24oic acid has been demonstrated. Cholestenone is present in feces and is a bacterial metabolite of cholesterol. Intestinal bacteria

have also produced 3-oxo-chol-4en-24oic acid from fecal bile-acids. The amount of steroidal estrogen produced by intestinal flora varies greatly from person to person but on average is believed much higher in people living on a normal Western diet than in those living on the low-fat diets common in Africa, Asia and South America. Since people living on a high-fat diet excrete on the average an estimated 600 mg per day of acid and neutral steroids, intestinal bacteria need aromatize only a very small proportion of this potential substrate to make a highly significant contribution to mammary carcinoma development. (18 references)

- 0612 RECENT ADVANCES IN IMMUNOLOGY OF CANCER: A REVIEW. (E.) Gangal, S. G. (Cancer Res. Inst. Bombay, India). *Indian J Cancer* 1(4):337-348, 1971.

Recent findings concerning the immunology of animal and human tumors are reviewed. Tumors induced by chemical carcinogens, radiation and viruses are discussed. Extensive investigations have been conducted on the phenomenon of immunity to tumors induced by 3-methylcholanthrene; serum antibodies to chemical carcinogen-induced tumors have been detected in immune animals. New cellular antigens have been found in solid tumors induced by viruses, and specific transplantation antigens have been shown to elicit resistance to challenge with viable tumor cells. Tumors induced by DNA viruses also show complement-fixing antigens. Five antigenic systems have been associated with virus-related murine leukemias. The phenomenon of tumor enhancement, in which grafted tumors grow vigorously in hosts which might have been expected to reject them, apparently requires the presence of a specific antibody which may block antigenic sites on tumor target cells. Specific antigens appear to be present even in some primary autochthonous tumors, a finding which indicates that primary tumor growth is related to two host factors: immunosuppression and specific immunological tolerance. Evidence of immune reactivity to tumors in man is provided by: spontaneous regression of tumors; increased tumor incidence in immunosuppressed patients; increased tumor incidence in patients with conditions associated with immunological deficiencies (e.g. ataxia teleangiectasia, Wiskott-Aldrich syndrome); depression of delayed hypersensitivity in cancer patients; and the finding of cancer-specific antigens in human colonic cancer. Furthermore, serological studies have shown that sera of Burkitt's lymphoma patients contain antibodies to Epstein-Barr virus. Presence of cell-mediated immune responses in humans has been suggested by the finding that DNA synthesis in lymphocytes of Burkitt's tumor is stimulated when lymphocytes are exposed to tumor cells. Despite the evidence, in men and animals, for specific immune responses to tumors, tumors continue to grow in hosts *in vivo*. This may be due to "antigen excess", in which the immune response of the host is quantitatively insufficient to react with excessive tumor antigen. (97 references)



- 0613 HERPES VIRUS INFECTIONS AND CANCER. (*Bul.*) Andonov, P. (Res. Inst. Epidemiol. Microbiol., Sofia, Bulgaria). *Suvr Med* 22(4):3-10, 1971.

The herpes virus (HV) group, which includes a large variety of viruses inducing a wide spectrum of diseases including neoplasia, is discussed. Host specificity, morphology, serological features, and epidemiology of HV infections, and their diagnosis, prevention and treatment as well as the relationship of HV to neoplastic diseases are reviewed. Reference is made to two main serological types of HV: type I includes the etiological agents for various non-genital infections; type II includes herpes genitalis. Reference is also made to 31 HV type I strains isolated by the author and four HV strains belonging to the herpes genitalis group, three of which had type II and one of which had intermediary immunological features. The oncogenicity of HV agents belonging to the DNA virus category is reviewed. The etiology of Burkitt's lymphoma and the relationship between infectious mononucleosis and leukemic disease are discussed. The necessity of further research on HV pathogenicity for animals and man is emphasized. (36 references)

- 0614 EVIDENCE FOR A HUMAN BREAST CANCER VIRUS. (*E.*) Moore, D. H. (Inst. Med. Res., Camden, N.J.). *Indian J Cancer* 8(2):80-83, 1971.

Methods of detecting the presence of oncogenic viruses are reviewed with special reference to the application of these methods to finding evidence that viruses cause cancer in man. Leukemia and breast cancer are two types of human malignancy which may be of viral origin. Electron microscopy of tissue from Parsi women with breast cancer has revealed particles identical in structure to those responsible for transmitting breast cancer in mice; in addition, these particles have been found in American women with family histories of mammary cancer. In immunological experiments, sera from breast cancer patients have been found to depress tumor incidence in mice given inoculations of viruses which had been treated with these sera. Methods for breaking open RNA viruses to isolate their RNA have permitted the determination of the characteristic sedimentation constants of RNA from tumor viruses. This enables researchers to compare the RNA from suspected human tumor viruses with that of viruses whose oncogenic capacity is known. The suggestion that the replication of the RNA tumor virus takes place through a DNA intermediate (the "provirus" theory), and the finding that viral RNA exists which acts as a template for synthesizing RNA ("inverse transcriptase") are two other recent discoveries which expand the possibilities for discovering a human tumor virus. Reverse transcriptase has been found to be confined almost exclusively to oncogenic viruses. Another means of testing the oncogenicity of a putative tumor virus is to determine the relationship of its nucleic acid to the nucleic acid of other viruses in hybridization experiments. (25 references)

- 0615 THE CUTIS AS A SITE FOR TUMOR DEVELOPMENT. (*It.*) Montagnani, A. (Trieste U., Italy). *Minerva Med* 62(54):2697-2704, 1971. (No references)

- 0616 DISTRIBUTION OF BLOOD GROUPS IN CANCER. (*E.*) Ghooi, A. M. (Gandhi Med. Coll., Bhopal, India), S. K. Kamalpuria, P. K. Jain and P. L. Tandon. *Indian J Cancer* 7(4):296-305, 1970. (41 references)

- 0617 OCCUPATIONAL CANCER. (*E.*) Clayson, D. B. (Leeds, England). *UICC Bull* 9(2):3, 1971. (No references)

- 0618 TUMORS AND NEPIOLOGY. (*It.*) Carratelli, G. (Rome, Italy). *Minerva Nipiol* 20(6):171-177, 1971. (19 references)

- 0619 NEW PHORBOL ESTERS AND RELATED COCARCINOGENS. (*E.*) Anonymous. *S Afr Cancer Bull* 15(2):66-68, 1971. (No references)

- 0620 HYPOTHESIS FOR THE VIRAL ONCOGENESIS OF GARDNER'S SYNDROME. (*E.*) Camiel, M. R. (State U. New York, Downstate Med. Ctr., Brooklyn), L. L. Alexander and D. L. Benninghoff. *J Nat Med Ass* 63(4):272-275, 1971. (35 references)

- 0621 CANCER AND AGING: THE EPIDEMIOLOGICAL EVIDENCE. (*E.*) Doll, R. (U. Oxford, England). *S Afr Cancer Bull* 15(2):51-52, 1971. (No references)

- 0622 GENETICS, SKIN AND CANCER CONTROL. (*E.*) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.), W. L. Harlan and A. J. Krush. *Amer Family Physician* 4(3):87-92, 1971. (No references)

- 0623 BRONCHOGENIC CARCINOMA: ANATOMICAL AND PHYSIOLOGICAL CONDITIONS OF ITS ORIGIN AND EVOLUTION: I. INTRODUCTION. CURRENT POSITION OF THE PROBLEM. (*E.*) Mucholda, F. (Fac. Med., Charles U., Prague, Czechoslovakia), Z. Borek and J. Lhotka. *Acta Univ Carol [Med]* Monograph 41:5-21, 1970. (106 references)

0624 ISOZYMES IN CANCER. (E.) Weinhouse, S.  
(Temple U. Sch. Med., Philadelphia, Pa.)  
*Cancer Res* 31(8):1166-1167, 1971. (No references)

0628 ETIOLOGY AND DIAGNOSIS OF POLYPS AND OF  
RECTAL-COLONIC POLYPOSIS. (Fr.) Paris, J.  
(Reg. Hosp., Lille, France) and A. Gerard. *Ann Chir*  
25(11-12):593-596, 1971. (References)

0625 THE ROLE OF ENVIRONMENTAL FACTORS IN THE  
PATHOGENESIS OF HUMAN TUMORS. CIGARETTE  
SMOKING. (It.) Leone, G. (Sant'Anna Hosp. Obstet  
and Gynec., Torino, Italy). *Minerva Med* 62(49):  
2461-2480, 1971. (47 references)

0629 POLYPS AND CANCER. (Fr.) Alexandre, J.-H.  
(Broussais Hosp., Paris, France). *Ann Chir*  
25(11-12):622-625, 1971. (7 references)

0626 THE "IMMUNOLOGY AND CANCER" COLLOQUIUM OF  
THE MERIEUX FOUNDATION. (Fr.) Trouillas,  
P. (No affiliation). *Lyon Med* 225(12):1263-1265,  
1971. (No references)

0627 INITIATION OF IMMUNE RESPONSES AGAINST  
CANCER CELLS. (E.) Metcalf, D. (Melbourne,  
Australia). *UICC Bull* 9(2):6, 1971. (No references)



# CHEMICAL CARCINOGENESIS

0630 GENETICS OF SOMATIC MAMMALIAN CELLS: XII: MUTAGENESIS BY CARCINOGENIC NITROSO COMPOUNDS. (E.) Kao, F. T. (U. Colorado Med. Ctr., Denver) and T. T. Puck. *J Cell Physiol* 78:139-144, 1971.

Cultures of Chinese hamster ovary cells (CHO-K1) were exposed to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in varying concentrations or to 3 of its carcinogenic derivatives: N-nitrosodimethylamine (NDMA) which causes liver cancer in rats, N-nitrosomethylurea (NMU) which causes gastric cancer in rats and N-nitrosomethylurethane (NMUT) which causes stomach cancer in rats. The effect of these nitroso compounds on cell survival, and their induction of auxotrophic mutations and chromatid exchanges, was observed. The mean lethal concentrations of the 4 compounds for CHO-K1 cells varied by a factor of  $5 \times 10^4$ ; 10% survival of treated cells was effected by 0.15 mg/ml of NMUT, by 125 mg/ml of NMU, and by 18,000 mg/ml of NDMA. Three of the carcinogens showed single-hit and one showed multiple-hit survival curves. The 4 nitroso compounds each produced between 0.084 and 0.108 chromatid breaks in CHO-K1 cells. All 4 carcinogens were active as inducers of auxotrophic mutant genes in CHO-K1 cells. The capacity of the 4 nitroso compounds to induce chromatid exchanges differed; MNNG produced more exchanges in lower concentrations than the 3 derivatives and NMUT was the least effective producer of chromatid exchanges.

0631 TRANSFER RNA METHYLASE ACTIVITY IN NORMAL MONKEY LIVER AND IN CARCINOGEN-INDUCED HEPATOMA. (E.) Waalkes, T. P. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), R. H. Adamson, W. O'Gara and R. C. Gallo. *Cancer Res* 31(8): 069-1073, 1971.

N-nitrosodiethylamine (DENA) was administered to normal healthy rhesus monkeys and periodic liver biopsies were taken and tested for premalignant change using the serum  $\alpha$ -fetoprotein test; a premalignant state was often indicated by a positive  $\alpha$ -fetoprotein test in advance of any overt sign of malignancy. Livers in a premalignant state, livers showing hepatoma, and normal livers were examined for tRNA methylase activity using tRNA from *Escherichia coli*, from normal adult monkey liver or from hepatoma as a methyl acceptor. In order of increasing magnitude, extracts of premalignant liver, newborn liver, and hepatoma, methylated normal and hepatoma monkey tRNA 1.5-3 times more than normal adult monkey liver extracts. Apparently, a change in the specificity of tRNA methylation occurred during carcinogenesis with DENA; since increased tRNA methylase activity was found in a premalignant liver it was concluded that changes in tRNA methylase accompany early malignant conversion. When *E. coli* tRNA was methylated by a combination of normal adult monkey liver extracts and hepatoma extracts, it was found that tRNA methylation by the combined extracts was less than what would have been expected from an examination of tRNA methylation by extracts run individually. Methylation of *E. coli*

tRNA by combinations of hepatoma plus newborn liver extracts, premalignant liver plus newborn liver extracts, and newborn liver plus monkey liver was as expected. This suggested that an inhibitor of tRNA methylase, absent from newborn liver and hepatoma extracts, was present in normal adult liver.

0632 CALCULATION OF THE  $\pi$ -ELECTRON "RING CURRENT" PROPERTIES OF SOME CARCINOGENIC, HEPTACYCLIC, CONDENSED, BENZENOID HYDROCARBONS. (E.) Mallion, R. B. (Math. Inst., U. Oxford, England). *J Med Chem* 14(9):824-826, 1971.

Calculations were reported on the magnetic effects arising from the induced  $\pi$ -electron ring currents in 5 carcinogenic, 7-ringed, condensed benzenoid hydrocarbons; compounds studied were: benzo[a]-naphtho-[2,1,8-*hi*j]naphthacene, benzo[a]naphtho[8,1,2-*cde*]naphthacene, tribenzo[a,c,j]naphthacene, dibenzo[h,rs]pentaphene and peropyrene. Ring current intensities were expressed relative to the magnitude of the ring current in benzene. The smallest ring current so far calculated in a condensed benzenoid hydrocarbon was 0.236 in benzo[b]perylene and the largest in a polycyclic molecule of 7 rings or less was 1.560 in the outer rings of coronene. All the ring currents in the 5 compounds tested fell just within this range. Although it had been observed that the more condensed a given ring the smaller the  $\pi$ -electron it bears, the central ring in peropyrene had a ring current intensity over 6 times that in the (formally) analogous central ring in perylene. Trends in the ring current intensities and proton chemical shifts were discussed. The "ring current" theory had been shown to account satisfactorily for observed chemical shifts in a wide range of benzenoid molecules, and the present calculations were thought to be a reliable aid in the analysis of experimental proton magnetic resonance (pmr) spectra of these hydrocarbons; pmr spectra may throw light on the electronic distribution of these molecules which is often thought to be involved in their carcinogenic effects.

0633 PHORBOL ESTER A<sub>1</sub>-INDUCED HYPERPLASIA: MORPHOLOGICAL STUDIES. (Ger.) Bach, H. (German Cancer Res. Center, Heidelberg) and K. Goerttler. *Virchow Arch Path Anat* 8(3):196-205, 1971.

Combined histometric and cytophotometric studies were carried out to investigate the transitory hyperplastic alterations of mouse skin following application of the biologically active phorbol ester fraction from croton oil. Experiments were carried

out with 85 NMRI 49-56-days-old female mice. Phorbol ester (PE) A<sub>1</sub> was applied topically (0.02  $\mu$ Mole in acetone solution) on the dorsal skin of 65 mice; 17 mice were treated likewise with plain acetone and were considered as controls. Animals were sacrificed at 17 different times from 0 to 240 hr after PE treatment. Each sacrificed group included 4 experimental and 1 control mouse. No skin alterations were observed in the mice treated with plain acetone. Cytophotometry of skin specimens from experimental mice revealed a nuclear volume increase 8 hr after application of PE; this increase reached a peak value 16 hr later and then gradually decreased to normal values 240 hr after the beginning of the experiment. The average DNA content of cell nuclei increased after 12 hr following PE treatment and remained at a level 20% greater than controls through 72 hr, then decreased to normal values at 240 hr. Histometry revealed deviations from the norm in terms of the number of nuclei per surface unit 12 hr following PE application, with peak deviations occurring between 16 and 36 hr and returning to normal towards the end of the experiment. Epithelial hyperplasia with inflammatory phenomena appeared to be evident by 24 hr and reached peak conditions 36-60 hr following treatment; the epidermis returned to normal towards the end of the experiment. The tumor promoting action of PE A<sub>1</sub> consists, possibly, of a carcinogen transfer promoting effect by means of induced temporary alterations of nuclear membrane permeability. The experiment is suggested to serve as a model for the testing of other cocarcinogens or true carcinogenic compounds.

- 0634 COMPARATIVE CARCINOGENICITY OF FORMIC ACID 2-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL] HYDRAZIDE AND RELATED CHEMICALS IN THE RAT. (E.) Ertürk, E. (U. Wisconsin Med. Sch., Madison), J. E. Morris, S. M. Cohen, A. M. Von Esch, A. J. Crovetti, J. M. Price and G. T. Bryan. *J Nat Cancer Inst* 47 (2):437-445, 1971.

The carcinogenic effects of formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide (FNT) and of 4 of its structural analogues were compared in male and female Sprague-Dawley rats and in female Buffalo rats; the 5 test compounds were administered in the rats' diet. FNT was highly carcinogenic in both rat strains; 25 of 26 rats given FNT developed multiple mammary tumors, 22 of 26 developed kidney tumors and 12 of 26 developed hepatic tumors. The structural analogue of FNT, 2-hydrazino-4-(5-nitro-2-furyl)thiazole was also highly carcinogenic, inducing mammary tumors in 15 of 16 treated rats and kidney tumors in 3 of 16 rats. Formic acid 2-[4-(2-furyl)-2-thiazolyl]hydrazide and 1-formyl-3-thiosemicarbazide were far less carcinogenic than the 2 preceding compounds; the former compound induced no tumors in 23 treated rats and the latter compound induced 5 solitary mammary tumors in 27 treated rats. Formic acid 2-(4-methyl-2-thiazolyl)hydrazide was intermediate in carcinogenicity; it induced 8 solitary mammary tumors in 28 treated

rats. These results suggested that the 5-nitro group of the furan ring, which is lacking in the relatively uncarcinogenic 2-[4-(2-furyl)-2-thiazolyl]hydrazide, plays a principal part in the carcinogenic process.

- 0635 ON THE ASSOCIATION BETWEEN PHOTODYNAMIC AND ENZYME-INDUCING ACTIVITIES IN POLYCYCLIC COMPOUNDS. (E.) Epstein, S. S. (Harvard Med. Sch., Boston, Mass.), N. P. Buu-Hoi and D.-P. Hien. *Cancer Res* 31(8):1087-1094, 1971.

Two hundred and forty polycyclic compounds were tested for photodynamic activity and for capacity to induce xoxazolamine hydroxylase in rats; in tests of photodynamic activity, the duration of radiation exposure required to kill *Paramecium caudatum* in the presence of test compounds was determined. Eighty-three polycyclic compounds had high photodynamic activity; the remaining 157 compounds had low photodynamic activity or were inactive. Of the 83 compounds with high photodynamic activity, 79 were active inducers of xoxazolamine hydroxylase; of 58 compounds which failed to induce hydroxylase, 54 showed weak photodynamic activity. But of 157 compounds with photodynamic activity only 103 were active enzyme inducers. It was estimated that compounds which were of high photodynamic activity had 10 times greater odds of inducing hydroxylase activity than compounds of low photodynamic activity. Chemical substitutions which enhanced photodynamic activity in polycyclic compounds were in general also favorable for enzyme induction by the compounds. Similarly, substitutions which reduced photodynamic activity suppressed enzyme-inducing potency as a rule. The basis for the association of photodynamic activity and enzyme-induction in polycyclic compounds is unknown.

- 0636 MUTAGENICITY OF N-NITROSOMORPHOLINE IN THE HOST-MEDIATED ASSAY. (E.) Zeiger, E. (FDA, Dept. Hlth., Educ., Welfare, Washington, D. C.) and M. S. Legator. *Mutat Res* 12:469-471, 1971.

Male Swiss albino mice were given i.p. injections of 2.0 ml of an exponential culture of *Salmonella typhimurium* followed by an i.m. injection of 0.1 ml of N-nitrosomorpholine (NM); in a related experiment, mice were given 0.5 ml NM by gavage prior to infection with *S. typhimurium*. Three hr after treatment, mice were killed and bacteria in peritoneal exudates were examined for genetic mutations. Although it had been established that NM was not mutagenic for *S. typhimurium* *in vitro*, NM was found to be mutagenic for the bacterium in the mouse peritoneal cavity. Mice given NM by injection, as well as mice given NM by gavage, showed a 50-fold increase in the frequency of *his*<sup>+</sup> revertants of *S. typhimurium*. Morpholine did not produce mutations in bacteria in mouse peritoneal cavities.



- 0637 EFFECT OF *BACILLUS CALMETTE-GUERIN* ON MAMMARY TUMOR FORMATION AND CELLULAR IMMUNITY IN DIMETHYLBENZ(a)ANTHRACENE-TREATED RATS. (E.) Piessens, W. F. (Free U. Brussels, Belgium), R. Heimann, N. Legros and J.-C. Heuson. *Cancer Res* 3;(8):1061-1065. 1971.

The effects of a single dose of *Bacillus Calmette-Guerin* (BCG) given at various times before and after a carcinogenic administration of 7,12-dimethylbenz(a)anthracene (DMBA) on the cellularity of the rat reticuloendothelial system (RES) and on tumor formation were observed. An experiment was devised to study the effect of DMBA and BCG on the RES by measuring the wt of the spleen and the total number of mononuclear cells in the spleen in rats given a single BCG injection 21 days before, on the same day as, or 7-42 days after, DMBA feeding (20 mg). In rats given DMBA but not BCG, DMBA produced a significant decrease in spleen wt; spleen wt reached a minimum on day 5 after DMBA and remained decreased until day 14, returning to normal by day 20. BCG given on the same day as DMBA counteracted the effect of DMBA on spleen wt; by day 14 after DMBA, the spleen wt in BCG-treated rats had surpassed that in controls given neither DMBA nor BCG. In rats given DMBA but not BCG, the number of mononuclear cells per spleen followed the same general pattern as spleen wt. However, the number of mononuclear spleen cells in these rats remained below control values through the latency period of 6 wk. BCG given 21 days before DMBA significantly reduced both amplitude and duration of the carcinogen-induced depression in the number of mononuclear spleen cells. However, the most striking effect was seen when BCG was given on the same day as DMBA; cell number per spleen increased immediately and significantly above control values for at least 10 days. In a related experiment, mammary carcinomas appeared 6 wk after administration of DMBA to rats not given BCG. BCG treatment markedly reduced the proportion of tumor-bearing rats, but only in the group in which BCG was given on the same day as DMBA; in this group 17 of 19 rats given DMBA but not BCG developed tumors while 6 of 20 rats given BCG as well as DMBA developed tumors. When BCG was administered after the appearance of the first tumor, it accelerated the formation of additional tumors. The ultimate tumor incidence was similar in BCG-treated and untreated rats. The effect of BCG on the induction of mammary tumors by DMBA did not seem to be mediated through endocrine mechanisms.

- 0638 INHIBITORY EFFECT OF VITAMIN A ON CARCINOGENESIS. (E.) Shamberger, R. J. (Cleveland Clin. Fdn., O.). *J Nat Cancer Inst* 47(3):667-673, 1971.

A study was performed to determine the effect of the lysosomal labilizers, vitamin A and filipin, and the lysosomal stabilizers, hydrocortisone and chloroquine, on the classical tumor-promoting system of 7,12-dimethylbenz(a)anthracene (DMBA)-croton oil;

the effect on the tumor-inhibiting or tumor-enhancing activity of numerous isoprenoid compounds was also studied. Groups of shaved ICR Swiss female mice were initiated once with a solution of DMBA applied to their backs. After 3 wk, test substances, or a mixture of croton resin, croton oil or phenol, and test substances, was applied to the skin 5 times per wk for 18 wk. Test substances included  $\beta$ -carotene,  $\beta$ -ionone, squalene, isoprene, retinyl acetate, retinol, filipin, hydrocortisone and chloroquine.  $\beta$ -carotene greatly increased the number of tumors produced when applied concomitantly with croton resin (53% increase in number of papillomas/mouse); by contrast, retinyl acetate strikingly reduced the number of tumors (76% reduction in tumor incidence). Squalene, isoprene and  $\beta$ -ionone reduced the number of papillomas, but not to the extent of retinyl acetate. No mice given isoprenoid compounds or DMBA alone had tumors. In a second experiment using croton oil,  $\beta$ -carotene increased the number of tumors by 29% and retinyl acetate reduced the number of tumors by the same amount. Retinol in one experiment reduced the number of papillomas by 75%; retinol also reduced the number of tumors in mice given DMBA and phenol. Filipin dramatically reduced the number of mice with tumors compared to controls; in controls, tumors arose at 8 wk after DMBA, while in filipin-treated mice, the first tumors were seen at 14 wk. After the lysosomal labilizers, filipin and vitamin A, were applied for 3 wk to DMBA-initiated mice, only a few tumors developed after the use of croton oil. Both groups of mice treated with the lysosomal stabilizers, chloroquine and hydrocortisone, had more tumors than controls. Acid phosphatase and aryl sulfatase activities were reduced in DMBA-initiated mouse skin treated with hydrocortisone and chloroquine.  $\beta$ -carotene also reduced acid phosphatase and aryl sulfatase activities. Acid phosphatase was significantly increased by the lysosomal labilizers, retinol and filipin.

- 0639 MOLECULAR CHARACTERISTICS OF SOME CARCINOGENIC HYDROCARBONS. (E.) Cavalieri, E. (Lab. Chem. Biodynamics, U. California, Berkeley) and M. Calvin. *Proc Nat Acad Sci USA* 68(6):1251-1253, 1971.

Photolysis of benzo(a)pyrene and 1-methylcytosine hydrochloride yielded 6-(1-methylcytos-5-yl) benzo(a)pyrene as the major product; the specific reactivity of the 6 position of the benzo(a)pyrene suggested that acid-catalyzed proton exchange reactions might be used to identify the relative reactivities of the various positions of benzo(a)pyrene. The kinetics of proton-deuterium exchange for various positions of benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene were therefore investigated. In benzo(a)pyrene, the proton at position 6 was readily exchanged, suggesting that this is the most nucleophilic position and the one to which the acid proton was first attached. Next in reactivity came position 1 which was followed by position 3. It was thought that the chemical reactivity induced in benzo(a)pyrene by hydroxylating enzymes might be due to the

generation of electrophilic centers in the hydrocarbon. Examination of proton-deuterium exchange activity in 7,12-dimethylbenz(a)anthracene revealed that the acid protons were first attached to the 7 and 12 positions, giving rise to nucleophilic reaction centers rather than to electrophilic ones, as in benzo(a)pyrene. Here the 12 position appeared to be the most basic one and the corresponding positive charge was localized on position 7. For methylcholanthrene the situation was similar to that of dimethylbenz(a)anthracene. It was suggested that activation of the benzo(a)pyrene by electrophilic attack on the 6-position by a positive oxygen atom produced by the action of the hydroxylase systems is followed by the reaction of position 1 or 3 as an electrophilic center on the suitable nucleophilic cellular component. In the other two hydrocarbons, the complementary reactive position was a nucleophilic center on the saturated carbon atom adjacent to the localized positive charge. Whether such reactions play a role in transforming cells from normal to malignant growth must be determined.

- 0640 MORPHOLOGICAL, ONCOGENIC, AND KARYOLOGICAL CHARACTERISTICS OF SYRIAN HAMSTER EMBRYO CELLS TRANSFORMED *IN VITRO* BY CARCINOGENIC POLYCYCLIC HYDROCARBONS. (E.) DiPaolo, J. A. (Nat'l. Cancer Inst., Bethesda, Md.), R. L. Nelson and P. J. Donovan. *Cancer Res* 31(8):1118-1127, 1971.

Hamster embryo cell cultures were exposed to one of three carcinogenic compounds: benzo(a)pyrene, 3-methylcholanthrene, or 7,12-dimethylbenz(a)anthracene (DMBA). The morphology and the karyologic pattern of transformed cultures were observed. Cell lines derived from colonies of hamster cells exposed to hydrocarbons showed a characteristic criss-cross arrangement of cells; this arrangement was taken to indicate morphological transformation of cultures. Cell cultures exposed to carcinogens were genetically stable. Cell lines were established from 62 recognized transformed cell cultures; as carcinogen-transformed cells were passaged *in vitro*, carcinogens washed out of transformed cells. Cell lines established from carcinogen-transformed colonies continued to show a criss-cross pattern of growth as well as nuclear pleomorphism. None of the three carcinogens tested produced a distinctive culture morphology in transformed cells; different cell lines produced by the same compound contained different types of cells. The cloning efficiency of transformed cells increased with age of the culture. When cells from carcinogen-transformed colonies were inoculated into weanling hamsters only those cell lines which were 50-75-days-old proved to be oncogenic; tumors produced were sarcomas. Untransformed cells failed to induce tumors in irradiated hamsters. Tumors induced by carcinogen-transformed cells were easily adapted to tissue culture and produced tumor cell lines. In chromosome studies, it was found that five transformed lines were hyperdiploid, four were hypodiploid and one was bimodal. Transformed cells showed a low incidence of chromosomal markers.

The most predominant chromosomal alterations in transformed cells were an increased number of acrocentric chromosomes and a loss of a member of the small metacentric chromosome. Distinctive large marker chromosomes included new metacentrics and a submetacentric. Carcinogen-transformed hamster cell lines rarely showed chromatid breaks, dicentric or fragments.

- 0641 STUDY OF THE POTENTIAL CARCINOGENICITY OF TOPICAL DRUG: SUGGESTIONS FOR A NEW EXPERIMENTAL APPROACH. (E.) Cioli, V. (Res. Labs., A.C.R., Rome, Italy), P. S. Barcellona and B. Silvestrini. *Exp Molec Path* 15:1-20, 1971.

3-Methylcholanthrene, bendazac, urethan and croton oil were applied topically to the scapular area of a total of 658 Swiss mice of both sexes; the induction of skin tumors and tumors in other locations was observed at 27 wk after initiation of treatment regimens. 3-Methylcholanthrene, applied biweekly for 1-3 wk in amounts of 0.1 ml, produced skin tumors in 21-61% of mice given 2 or 6 applications of the carcinogen, and produced non-skin tumors in 18-59% of these mice. Urethan produced no skin tumors when applied with acetone but did produce systemic tumors (including lung adenocarcinomas) in 57% of mice. Applied with croton oil, urethan produced skin papillomas. Bendazac produced no skin tumors when applied either alone or with croton oil; application of bendazac together with urethan was also without carcinogenic effect in the skin of treated mice.

- 0642 MOLECULAR-SIZE-DEPENDENT EFFECTS OF POLYNUCLEAR HYDROCARBONS ON MIXED-FUNCTION OXIDASES: POSSIBLE ACTION ON CASCADE-COUPLED OPERONS. (E.) Argus, M. F. (USPHS Hosp., New Orleans, La.), R. T. Valle, N. Venkatesan N. P. Buu-Hoi and J. C. Arcos. *First European Biophysics Congress Proc* 187-192, 1971.

Repression of dimethylnitrosamine (DMN) demethylase by 42 hydrocarbons was studied *in vivo* in weanling rats given i.p. injections of hydrocarbons at levels equimolar to 40 mg of 3-methylcholanthrene/kg body wt. Enzyme determinations in livers were performed 22-24 hr postinjection. The 3 most effective inhibitors of DMN-demethylase were 1,2,5,6-dibenzofluorene, 1,2,5,6-dibenzanthracene and 1,2,3,4-dibenzanthracene. The molecule size requirement for repression of DMN-demethylase was practically identical to that for induction of aminoazo dye N-demethylation (i.e., 85-100 Å<sup>2</sup>). The requirements of molecular geometry overlapped also with respect to molecular shape, as indicated by the low activity of triphenylene and coronene and the inactivity of ovalene. Coplanarity appeared to be an even more stringent requirement for



repression than for induction. The activities of hydrocarbons to induce or to repress microsomal enzyme synthesis were found to be in a mirror-image relationship. It was thought that inducible and repressible microsomal oxidase levels may have been regulated by cascade-coupled operons.

0643 IMBALANCES IN DNA AND HISTONE SYNTHESIS IN THE RAT LIVER DURING NEONATAL CARCINOGENESIS INDUCED BY DIMETHYLNITROSAMINE. (E.)

Gronow, M. (Dept. Exp. Path. Cancer Res., U. Leeds, England). *Europ J Cancer* 7:341-348, 1971.

Newborn rats were given 125 µg of dimethylnitrosamine (DMN) s.c. in the dorsal region; the effects of DMN on the rate of synthesis of liver DNA and histones were examined in 3- and 5-day-old rats. There was a considerable depression in the incorporation of <sup>3</sup>H-TdR into liver DNA 48 hr after DMN administration. In 3-day-old rats not given DMN, DNA synthesis activity measured 195 DNA counts/min/mg x 10<sup>-3</sup>, while DMN-treated rats showed 30 DNA counts/min/mg x 10<sup>-3</sup>. This decrease was still apparent at 96 hr after treatment with DMN. A decrease in the rate of histone synthesis, as indicated by the lower specific activity in histone fractions was seen in rats given DMN. However the effect of DMN on histones was not as marked as the effect of DMN on DNA. The most marked effect of DMN was on the F2a histone fraction; 3-day-old untreated rats showed 1548 counts/min/mg of histone synthesis activity in this fraction, while treated 3-day-olds showed 319 counts/min/mg. The F3 histone fraction also showed a significant decrease in specific activity in DMN-treated rats. In a related experiment, the effects of DMN on DNA synthesis and histones in the livers of post-weanling (4-5-wk-old) rats were observed. The liver DNA in post-weanling rats which had been treated at birth with DMN showed a 3-fold increase in specific activity over controls. Synthesis of F1, F2a and F2b histones was slightly inhibited by DMN, and the F3 histone showed a significant decrease in DMN-treated postweanling rats.

0644 ULTRASTRUCTURAL NUCLEOLAR SEGREGATION AND CARCINOGENICITY AMONG THE 4-NITROQUINOLINE-1-OXIDES. (E.) Paul, J. S. (U. Texas, Southwestern Med. Sch., Dallas), W. B. Ross and P. O'B. Montgomery. *J Nat Cancer Inst* 47(2):367-375, 1971.

Chang liver cells were treated with either 4-nitroquinoline-1-oxide (4-NQO), or each of 12 carcinogenic, mildly carcinogenic or noncarcinogenic derivatives of 4-NQO; following exposure to the test compound, liver cells were prepared for electron microscopic examination. 4-NQO and 4 of its carcinogenic derivatives induced marked nucleolar segregation in nucleoli of exposed liver cells. Thirty min after introduction of 4-NQO or a carcinogenic derivative,

dark nucleolar plaques, formed from the coalescence of electron-opaque particles derived from the nucleolonema, were seen scattered throughout the nucleoli. By 1-2 hr after exposure to the test compound, these plaques migrated toward the periphery of nucleoli; at this point the distinction between nucleolonema and pars amorpha was not detectable. After 4 hours, these plaques fused into fewer and more homogeneous "dark caps". Less electron-dense particles were also seen in nucleoli exposed to 4-NQO or its carcinogenic derivatives. All the carcinogenic derivatives of 4-NQO decreased the size of the nucleoli during nucleolar segregation in exposed liver cells. Weakly carcinogenic derivatives of 4-NQO produced fewer fully-formed nucleolar caps than did more carcinogenic derivatives. Non-carcinogenic derivatives of 4-NQO did not induce nucleolar segregation; nucleoli in cells exposed to non-carcinogenic derivatives showed a normal ultrastructure.

0645 OIL CANCER IN THE SAVOY ALPS AND THE BIRMINGHAM REGION: A COMPARISON. (E.)

Kipling, M. D. (No affiliation). *Trans Soc Occup Med* 21(3):73-78, 1971.

0646 OBSERVATIONS ON THE PLASMA AMINO ACIDS OF PATIENTS WITH ACUTE LEUKEMIA. (E.)

Rudman, D. (Emory U. Sch. Med., Atlanta, Ga.), W. R. Vogler, C. H. Howard and G. G. Gerron. *Cancer Res* 31(8):1159-1165, 1971.

0647 ALDRIN AND DIELDRIN IN HUMAN BLOOD COMPONENTS. (E.) Mick, D. L. (Coll. Med., U. Iowa, Iowa City), K. R. Long, J. S. Dretchen and D. P. Bonderman. *Arch Environ Health* 23:177-180, 1971.

0648 EVIDENCE OF ANTITUMORGENIC EFFECTS OF DDT.

(E.) Laws, E. R. (Johns Hopkins Hosp., Baltimore, Md.). *Arch Environ Health* 23:181-184, 1971.

0649 TRANSPLACENTAL ACTION OF 3-METHYLCHOLANTHRENE AND BENZO(a)PYRENE ON 4 GENERATIONS OF MICE. (Rus.) Andrianova, M. M. (Acad. Med. Sci., Moscow, U.S.S.R.). *Bull Eksp Biol Med* 71(6):81-84, 1971.

- 0650 THE ACTION OF NITROSOMETHYLUREA AND DIMETHYLNITROSAMINE ON MOUSE EMBRYO LUNG TISSUE CULTURES. (Rus.) Smetanin, E. Ye. (Acad. Med. Sci., Moscow, U.S.S.R.). *Bull Eksp Biol Med* 71(6):77-81, 1971.
- 0651 COMPOSITION STUDIES ON TOBACCO: XLIV. TUMOR-PROMOTING ACTIVITY OF SUBFRACTIONS OF THE WEAK ACID FRACTION OF CIGARETTE SMOKE CONDENSATE. (E.) Bock, F. G. (Roswell Park Mem. Inst., Buffalo, N.Y.), A. P. Swain and R. L. Stedman. *J Nat Cancer Inst* 47(2):429-436, 1971.
- 0652 ELECTRON MICROSCOPIC LOCALIZATION OF ACRIDINE ORANGE BINDING TO DNA WITHIN HUMAN LEUKEMIC BONE MARROW CELLS. (E.) Frenster, J. H. (Stanford U. Sch. Med., Calif.). *Cancer Res* 31:1128-1133, 1971.
- 0653 TUMOR-PROMOTING ACTIVITY OF PHORBOL AND FOUR DIESTERS OF PHORBOL IN MOUSE SKIN. (E.) Baird, W. K. (U. Wisconsin Med. Ctr., Madison) and R. K. Boutwell. *Cancer Res* 31:1074-1079, 1971.
- 0654 METABOLIC PROPERTIES OF MOUSE TRANSPLANTABLE ADENOCARCINOMAS: II. SUBSTRATE UTILIZATION BY HOMOGENATES. (E.) Floridi, A. (Regina Elena Inst. Cancer Res., Rome, Italy) and A. Caputo. *J Nat Cancer Inst* 47(2):271-275, 1971.
- 0655 MYCOLOGICAL AND SEROLOGICAL STUDIES ON *ASPERGILLUS FLAVUS* ISOLATED FROM PARANASAL ASPERGILLOMA IN SUDAN. (E.) Mahgoub, E. S. (Fac. Med., U. Khartoum, Sudan). *J Trop Med Hyg* 74(7):162-165, 1971.
- 0656 METABOLISM AND BILIARY EXCRETION OF N-2-FLUORENYLACETAMIDE AND N-HYDROXY-2-FLUORENYLACETAMIDE. (E.) Levine, W. G. (Albert Einstein Coll. Med., Yeshiva U., Bronx, N.Y.). *Life Sci* 10(13):727-735, 1971.
- 0657 STUDIES ON THE SHIFT IN THE pH OPTIMUM OF HEPATIC MICROSOMAL ANILINE *p*-HYDROXYLATION FOLLOWING TREATMENT OF RATS WITH 3,4-BENZOPYRENE. (E.) Hansen, A. R. (Coll. Med., U. Iowa, Iowa City) and J. R. Fouts. *Chem Biol Interact* 3:123-129, 1971.
- 0658 TUMOUR INDUCTION BY LOW MOLECULAR WEIGHT ALKYLATING AGENTS. (E.) Frei, J. A. (Fac. Med., U. Western Ontario, London, Canada). *Chem Biol Interact* 3:117-121, 1971.
- 0659 SIGNIFICANCE OF BOUND DYE AND GLUTATHIONE FOR AMINOAZO DYE HEPATOCARCINOGENESIS. (E.) Neish, W. J. P. (Dept. Pharmacol. Therap., U. Sheffield, England). *Chem Biol Interact* 3:109-116, 1971.
- 0660 EFFECT OF PERINATAL ADMINISTRATION OF 7,12-DIMETHYLBENZ(a)ANTHRACENE ON THE LATER RESPONSE TO A SUBCUTANEOUS TEFLON IMPLANT. (E.) Tomatis, L. (Int. Agency Res. Cancer, Lyon, France) and L. Parmi. *Tumori* 57:55-62, 1971.
- 0661 THE EFFECT OF BENZENE ON HUMAN HEMOGLOBIN (Ger.) Lampe, J. (Ernst-Moritz-Arndt U., Greifswald, Germany), J. Behlke, W. Graf, K. Müller and W. Scheler. *Acta Biol Med German* 26(5):911-916, 1971.
- 0662 THE FREQUENCY OF ASBESTOS BODIES IN HUMAN LUNGS. (Ger.) Nizze, H. (Schwerin Reg. Hosp., Germany). *Int Arch Arbeitsmed* 28(1):71-82, 1971.
- 0663 ALVEOLAR MACROPHAGES: STRUCTURAL AND FUNCTIONAL DIFFERENCES BETWEEN NONSMOKERS AND SMOKERS OF MARIJUANA AND TOBACCO. (E.) Mann, E. G. (Mount Zion Hosp., San Francisco, Calif.), A. B. Cohen, T. N. Finley and A. J. Ladman. *Lab Invest* 25(2):111-120, 1971.



0664 EFFECTS OF VARIOUS HYDRAZINES UPON THE METABOLISM OF GAMMA AMINOBUTYRIC ACID (GABA)-1-<sup>14</sup>C BY RATS. (E.) Dost, F. N. (Sci. Res. Inst., Oregon State U., Corvallis), D. J. Reed and C. H. Wang. *Biochem Pharmacol* 20:1702-1707, 1971.

0665 AFFINITY LABELING AND CROSS-LINKING OF THE HEAVY AND LIGHT CHAINS OF A MYELOMA PROTEIN WITH ANTI-2,4-DINITROPHENYL ACTIVITY. (E.) Givol, D. (Weizmann Inst. Sci., Rehovot, Israel), P. H. Strausbauch, E. Hurwitz, M. Wilchek, J. Haimovich and H. N. Eisen. *Biochemistry* 10(18):3461-3466, 1971.

0666 MALIGNANT DEGENERATION OF LICHEN PLANUS. (E.) Kronenberg, K. (U. Illinois Hosp., Chicago), D. Fretzin and B. Potter. *Arch Derm* 104(3):304-307, 1971.

0667 METABOLIC STUDIES ON THE MECHANISM OF URETHAN ACTION V. SEQUENTIAL METABOLIC CHANGES IN URETHAN TREATED SWISS MICE WITH REFERENCE TO NUCLEIC ACID METABOLISM. (E.) Giri, C. P. (Cancer Res. Inst., Bombay, India) and S. V. Bhide. *Indian J Cancer* 7(2):119-125, 1970.

0668 HISTOPATHOLOGIC LESIONS IN CUTTHROAT TROUT (*Salmo clarki*) EXPOSED CHRONICALLY TO THE INSECTICIDE ENDRIN. (E.) Eller, L. L. (U.S. Dept. Interior, Columbia, Mo.). *Amer J Path* 64(2):321-330, 1971.

0669 GLUCOSE-6-PHOSPHATASE ACTIVITY IN RAT LIVER PARENCHYMA DURING AZO-DYE CARCINOGENESIS. (E.) Moulin, M.-C. (Montreal Cancer Inst., Quebec, Canada) and R. Daoust. *Int J Cancer* 8:81-85, 1971.

0670 EXAMINATION OF THE TUMOUR GROWTH PROMOTING EFFECT OF  $\epsilon$ -N-TRIMETHYLLYSINE: AN AUTO-RADIOGRAPHIC STUDY. (E.) Kopper, L. (Simmelweiss Med. U., Budapest, Hungary), B. Szende, K. Lapis and E. Tyihak. *Neoplasma* 18(3):251-256, 1971.

0671 SOME EFFECTS OF 3-METHYLCHOLANTHRENE ON URIDINE DIPHOSPHATE GLUCURONYLTRANSFERASE IN THE RAT AND GUINEA PIG. (E.) Howland, R. D. (Dept. Pharmacol., U. California, San Francisco) and A. Burkhalter. *Biochem Pharmacol* 20:1463-1470, 1971.

0672 ACID PHOSPHATASE AND DEOXYRIBONUCLEIC ACID STUDIES IN D.M.B.A. INDUCED EXPERIMENTAL ORAL CARCINOGENESIS IN HAMSTER CHEEK POUCH. (E.) Bharadwaj, V. P. (S.N. Med. Coll., Agra, India) and U. K. Luthra. *Indian J Med Res* 59:401-412, 1971.

See also:

- \* (Rev): 0604, 0610, 0617, 0619
- \* (Viral): 0691, 0719
- \* (Immun): 0755
- \* (Path): 0792
- \* (Epid-Biom): 0820

- 0673 CYTOPLASMIC DNA IN  $^{90}\text{Sr}$ -INDUCED RAT CHLOROLEUKEMIA. (E.) Nakai, G. S. (U. New Mexico Sch. Med., Albuquerque), M. E. Gaganig, R. O. Kelley and R. B. Loftfield. *Europ J Clin Biol Res* 16(6):560-563, 1971.

DNA from  $^{90}\text{Sr}$ -induced rat chloroleukemia cells was labeled "in vitro" with  $^3\text{H}$ -thymidine and separated into cytoplasmic and nuclear fractions. Nuclear and cytoplasmic DNA were centrifuged through sucrose density gradients. An 8S component was consistently found in cytoplasm; the component appeared to have no counterpart in the nucleus. Cytoplasmic DNA incorporated  $^3\text{H}$ -thymidine and constituted about 2.8% of total cellular DNA. The buoyant density of 8S DNA was 1.692, while the buoyant density of mitochondrial DNA was 1.697. Thus, the 8S DNA being linear with a different buoyant density made it unlikely that the 8S DNA was a degradation product of mitochondrial DNA. Electron microscope autoradiography was also used to distinguish cytoplasmic from nuclear DNA.

- 0674 THE INDUCTION OF LEUKEMIA AND LIFE SHORTENING IN MICE BY CONTINUOUS LOW-LEVEL EXTERNAL GAMMA RADIATION. (E.) Warren, S. (New England Deaconess Hosp., Boston, Mass.) and O. Gates. *Radiat Res* 47(2):480-490, 1971.

Strain RAP and strain A/Jax mice were exposed to low levels (0.062 rads/day) of cobalt  $\gamma$ -irradiation through 5 successive generations; irradiation was delivered from an external source. A series of mice used for comparative studies received  $\gamma$ -irradiation at high rates from an internal source in the thorax; controls were not irradiated. The incidence of leukemia in irradiated mice was observed. In externally irradiated RAP mice there was no significant difference in the incidence of leukemia from generation to generation. The overall incidence of leukemia in RAP mice, in all generations, was 54.7%, as compared to an incidence of 15.7% in internally irradiated RAP mice, and an incidence of 7.2% in unirradiated controls. None of the irradiated A/Jax mice developed leukemia. The mean age at which leukemia appeared in externally irradiated mice was 397 days (420 days for controls). Up to 400 days of age, there was little difference in the rate of death between externally irradiated and control mice; between 400-500 days, however, externally irradiated mice died more rapidly than controls. Of externally irradiated mice developing leukemia, 60% developed lymphatic leukemia, 25% developed myelogenous leukemia, and 18% developed leukemias of other types. Of internally irradiated mice developing leukemia, 90% developed lymphatic leukemia, none developed myelogenous leukemia, and 10% developed other leukemias. Of controls developing leukemia, 78% developed lymphatic leukemia, 28% developed myelogenous leukemia, and none developed other leukemias.

- 0675 DERMAL CYLINDROMA FOLLOWING X-RAY EPILATION OF THE SCALP. (E.) Black, M. M. (St. John's Hosp., London, England) and E. W. Jones. *Brit J Derm* 85:70-72, 1971.

- 0676 EARLY MANIFESTATION OF ANAPLASTIC THYROID CANCER AFTER RADIOIODINE TREATMENT FOR TOXIC NODULAR GOITER. (E.) Nemec, J. (Res. Inst. Endocrin., Charles U., Prague, Czechoslovakia), B. Niederle, V. Cenková, S. Vana and V. Zeman. *Neoplasma* 18(3):325-333, 1971.

- 0677 THOROTRAST-INDUCED ENDOTHELIAL CELL SARCOMA OF LIVER. (E.) Howard, R. J. (U. Minnesota Hlth. Sci. Ctr., Minneapolis), E. P. Todd, R. H. Dietzman and R. C. Lillehei. *Minn Med* 54(9):685-688, 1971.

- 0678 MYELOSIS WITH TERMINAL BLASTIC GROWTH IN A PATIENT WHO HAD UNDERGONE THOROTRAST ARTERIOGRAPHY TWENTY-ONE YEARS PREVIOUSLY. (Fr.) Andre, R. (St. Antoine Hosp., Paris, France), G. Duhamel, Y. Najean, A. Najman and A. Faille. *Ann Med Intern* 122(6-7):731-735, 1971.

- 0679 CARCINOMA OF THE PANCREAS AFTER ANGIOGRAPHY WITH THOROTRAST. (Ger.) Kleinschmidt, H. Y. (City Hosp. Inst. Pathol. Berlin, Germany). *Deutsch Gesundh* 26(3):1449-1450, 1971.

See also:

- \* (Viral): 0719, 0737  
\* (Immun): 0750, 0768, 0780



0680 DNA-DEPENDENT DNA POLYMERASES FROM HELA CELL NUCLEI: II. TEMPLATE AND SUBSTRATE UTILIZATION. (E.) Schlabach, A. (Roche Inst. Molec. Biol., Nutley, N. J.), B. Fridlender, A. Bolden and A. Weissbach. *Biochem Biophys Res Commun* 44(4):879-885, 1971.

Two well-differentiated DNA polymerase activities, designated nuclear enzyme I and nuclear enzyme II, found in HeLa cell nuclei, were examined; nuclear enzyme II resembled a single DNA polymerase found in HeLa cytoplasm. The HeLa cell DNA polymerases were dependent on the presence of DNA as primer and showed no activity in the absence of added template. The products of DNA synthesis by the 2 enzymes were completely (i.e., >98%) solubilized by pancreatic deoxyribonuclease. The DNA requirement could not be substituted for by RNA since none of the HeLa cell DNA polymerases could use RNA as template. The best DNA primer for each of the 2 nuclear DNA polymerases was nicked native DNA, i.e., DNA in which 3'-hydroxyl termini had been introduced by the action of pancreatic deoxyribonuclease. Heat denaturation of nicked native DNA rendered it at least 50% less effective as a primer. This indicated that, in addition to a requirement for 3'-hydroxyl termini, the nuclear enzymes needed some double-stranded structure for optimal priming activity. Neither of the 2 enzymes could use a polyribonucleotide strand as template. The ability of HeLa cell DNA polymerases to use a number of synthetic templates was studied; the enzymes differed in their ability to use synthetic polydeoxyribonucleotides as templates. With dAT and polydeoxyguanylate:polydeoxycytidylate as templates, nuclear enzyme I showed a 2-4-fold higher rate of synthesis than did nuclear enzyme II or the cytoplasmic enzyme. Polydeoxythymidylate:polyriboadenylate showed significant template activity only with nuclear enzyme I. The HeLa DNA polymerases described were unlike RNA-dependent DNA polymerases of RNA tumor viruses in that RNA did not serve as template for any of the HeLa enzymes.

0681 INTERACTIONS OF AVIAN SARCOMA VIRUS WITH RAT EMBRYO CELLS IN CELL CULTURE. (E.) Kotler, M. (McArdle Lab., U. Wisconsin, Madison). *J Gen Virol* 12:199-206, 1971.

Evidence was found that rat embryo cells converted by B77 avian sarcoma virus did not produce virus, though transformed cells contained the complete viral genome. B77 virus-converted rat cells in media were centrifuged to concentrate any possible virus 100-fold; concentrated virus-converted cells were tested for infective centers on secondary cultures of rat, mouse and chicken cells with or without the aid of UV- or  $\beta$ -propiolactone-inactivated Sendai virus. Since no foci were found on the assay cells, it was concluded that the B77 virus-converted rat cells did not produce virus. It was also found that concentrated B77 virus from converted rat cells

did not interfere with infection by B77 virus. To show that the B77 virus-transformed rat cells contained the complete viral genome, transformed rat cells were cloned. Cells from each clone and subclone were fused with chicken embryo cells and rescued viruses were tested on chicken and rat cells. All clones and subclones contained B77 virus capable of converting chicken and rat cells. In a related experiment, B77 virus-transformed rat cells from each of 5 clones were fused with the aid of inactivated Sendai virus with chicken embryo cells; the 5 clones of rat cells originated from the same parental cell. Five lines of virus were rescued and titrated on chicken and rat cells. Different clones of virus had different plating efficiencies. This suggested that changes in the virus genome were induced during maintenance and replication of virus in rat cells. Infection of rat cells by B77 virus was followed by morphological conversion of some cells. Other cells contained the virus genome but were not transformed; these cells were designated "abortively infected" cells.

0682 CELLULAR DNA SYNTHESIS ASSOCIATED WITH SHOPE FIBROMA VIRUS INFECTION. (Fr.) Jacquemont, B. (No affiliation) and L. Gazzolo. *C R Acad Sci [D] (Paris)* 273(2):253-256, 1971.

RK 13 strain rabbit kidney cell monolayer cultures were inoculated with  $10^{-6}$ - $10^{-1}$  UFF/cell of Shope fibroma virus (OA strain) to study the dynamics of DNA synthesis. Inhibition of DNA synthesis during the first 2 days was followed by an enhanced rate of DNA synthesis starting the 3rd day after viral inoculation. Extraction and separation of viral DNA from cellular DNA showed 80% of DNA synthesis occurring within the cell nuclei. The enhanced synthesis of DNA was directly related to the amounts of the inoculated virus and coincided with the formation of stacked cell foci. This phenomenon could be due either to the formation of stacked foci or to a certain "factor" produced by the infected cells. This factor could be responsible for the proliferative processes occurring in rabbits following viral inoculation *in vivo*.

0683 SYNTHESIS OF VIRUS-SPECIFIC RIBONUCLEIC ACID IN KB CELLS INFECTED WITH TYPE 2 ADENOVIRUS. (E.) Lucas, J. J. (Sch. Med., U. Pennsylvania, Philadelphia) and H. S. Ginsberg. *J Virol* 8(2):203-214, 1971.

Using DNA-RNA hybridization tests, virus specific RNA (cRNA) was found 6 hr after infection of KB cells with adenovirus type 2; this cRNA was found in extracts of total RNA from cells infected in the presence of 2  $\mu$ M 5-fluorodeoxyuridine (FUDR). In the absence of FUDR, there was a continuous increase in the incorporation of  $^3$ H-uridine into viral cRNA lasting until 20 hr after infection; at this time, about 40% of  $^3$ H-uridine entering RNA was found in cRNA. To detect

cRNA much earlier than 6 hr after adenovirus infection, experiments were designed to obtain RNA enriched with respect to viral cRNA species. Cytoplasmic extracts of infected cells were centrifuged on sucrose density gradients; RNA obtained from fractions in the polyribosome region of the gradient were used in the annealing reactions. Using RNA from polyribosome fractions, virus-directed transcription was detected at 3 hr after virus infection (i.e., 3-4 hr before initiation of viral DNA synthesis). To determine whether species of early virus-specific RNA were transcribed or were present late in infection, and conversely whether so-called late RNA species were present before replication of viral DNA, pre-saturation hybridization-inhibition analyses were performed. Three hybridization inhibition techniques, differing in the manner in which the DNA-RNA complex was isolated after the first hybridization reaction, were used. Different degrees of inhibition were measured by different tests. Data suggested that the initial hybridization with competing RNA frequently resulted in areas of limited hybridization and residual loops and tails of RNA which, if not removed, could effectively but nonspecifically compete with subsequent hybridization of the labeled virus-specific RNA. The variation in observed inhibition could be eliminated by alkali-degradation to a uniform size (4S) of inhibitory RNA species prior to hybridization. Undegraded RNA could be used if the DNA-RNA complex was isolated in a procedure which included rigorous washing and ribonuclease treatment before the second hybridization with labeled RNA. Using the rigorous hybridization-inhibition method, 3 classes of cRNA species were distinguished: (1.) early RNA class I whose synthesis began before viral DNA replication and stopped after initiation of DNA replication (class I comprised about 70% of early RNA and was degraded by 18 hr after adenovirus infection); (2.) early RNA class II whose synthesis began before viral DNA replication and continued at an enhanced rate late in infection; (3.) late RNA whose synthesis began after the initiation of viral DNA synthesis.

- 0684 C-TYPE RNA TUMOUR VIRUS GENOME EXPRESSION IN WILD HOUSE MICE. (E.) Gardner, M. B. (U. Southern California Sch. Med., Los Angeles), J. E. Officer, R. W. Rongey, J. D. Estes, H. C. Turner and R. J. Huebner. *Nature* 232(5313):617-620, 1971.

Wild house mice trapped in an urban area were given s.c. injections of 150 or 300 µg 3-methylcholanthrene (MC); a control group was given trioctanoin. Seventy-three percent of mice given MC developed tumors at the inoculation site; tumor tissue and spleen extracts from tumor-bearing mice were tested for indigenous virus by complement fixation (CF). All inoculated mice remained free of antibodies to 11 indigenous murine viruses. When a highly specific but narrow range murine sarcoma virus rat serum pool selected to contain antibodies reactive only with

the species specific major (gs-1) antigen was used, antigen in low titer was found in 10% of wild mouse tumors and in none of the wild mouse spleens. Spleens from 14% of control mice contained gs antigen. Tumor tissues and spleens were stored for 1 yr and re-tested with a more broadly reactive murine sarcoma virus serum pool; under these circumstances, positive CF reactions were seen in 32% of tumors, in 23% of spleens, and in none of the spleens of controls. C-type virus particles were found by electron microscopy in MC-induced tumor and in spleen from 12% of tumor-bearing mice; C-type particles were not found in any of 20 spleens from controls. Intracisternal A-type particles were found in some MC-induced tumors. In related experiments, older wild mice (i.e., about 19-20-mo.-old) were given MC and tested for presence of virus. A murine sarcoma virus pool of intermediate sensitivity, which contained antibodies against the species-specific major component (gs-1), as well as antibodies against an interspecies cross reacting component (gs-3) of the gs antigen complex, was used. Fifty-five percent of tumor extracts from these older mice contained gs antigen compared with 13% of MC-induced tumor extracts from younger mice. Eight spontaneous lymphomas arose in older mice; using broadly reactive murine sarcoma virus serum pools which contained high titers of antibodies to species specific and interspecies gs antigen, CF reactions were seen in spleen and/or tumor in all 8 lymphomatous mice. C-type particles were seen in 5 of 6 lymphomatous mice examined. These findings appeared to demonstrate the presence of the C-type RNA tumor virus genome in tissues of feral wild house mice unexposed to laboratory infection or to manipulated breeding.

- 0685 ALTERATIONS IN THE SUSCEPTIBILITY OF CULTURED MOUSE CELLS TO TRANSFORMATION BY MURINE SARCOMA VIRUS (HARVEY). (E.) Baker, R. S. U. (Sch. Med., Perth, Western Australia) and P. J. Simons. *J Gen Virol* 12:95-104, 1971.

Three phases of growth were seen in subcultured Balb/C mouse embryo cells; cells in the different phases were tested for their ability to support murine sarcoma virus (Harvey) (MSV) focus formation. An initial period of active growth was followed by a rapid decline in cell growth rate; there was negligible growth for a period extending from the 7th cell passage to the 14th passage. This phase was followed by a rapid improvement in growth rate which led to the establishment of a cell line. At the 10th passage a new line of cells (the "low line") was started. Incorporation of [<sup>3</sup>H]thymidine during successive subcultures paralleled changes in growth rate at the various cell passages. There were considerable differences in susceptibility to transformation by MSV with increasing passage level. First passage cells showed about 65 MSV foci/assay dish, while no foci were seen on 6th passage cells. No foci were seen on cells of the 9th through 22nd passages. When low-line cells in the 23rd and 29th passages were infected with MSV, they gave focus



counts 2-3 times greater than those obtained with passage 1 cells of the same line. It was noted that primary cells were more susceptible to MSV than would be expected from their rate of growth. Non-dividing (amitotic) cells were not susceptible to MSV transformation.

- 0686 EXTENT OF TRANSCRIPTION BY THE RNA-DEPENDENT DNA POLYMERASE OF ROUS SARCOMA VIRUS. (E.) Varmus, H. E. (Dept. Microbiol., U. California, San Francisco), W. E. Levinson and J. M. Bishop. *Nature New Biology* 233(35):19-21, 1971.

The reassociation kinetics of RNA-dependent DNA polymerase produced double stranded DNA of Rous sarcoma virus, was investigated. Rates of reassociation were determined by denaturing a double stranded DNA sample in a boiling water bath and frequently removing samples for analysis on hydroxyapatite. Denaturation was complete at the start of the experiment and reassociation proceeded rapidly, with a  $C_0t$  value at the 50% reassociation point of about  $1.7 \times 10^{-3}$  mol-s/l ( $C_0t$  = starting concentration of DNA x time).

The population of DNA molecules was relatively homogeneous, but reassociation did not progress significantly beyond 85%. Results indicated that 85-90% of the double stranded product represented a small portion (about 5%) of the genome. It was proposed that the viral genome is equivalent to a 36S subunit or that only single stranded DNA present in the intermediate hybrid structures contains sequences homologous to the complete RNA genome.

- 0687 IMMATURE PARTICLE FORMATION OF YABA POXVIRUS STUDIED BY ELECTRON MICROSCOPY. (E.) Tsuruhara, T. (Natl. Inst. Hlth., Tokyo, Japan). *J Nat Cancer Inst* 47(3):549-551, 1971.

Cynomolgous monkeys were inoculated i.d. with suspensions of Yaba poxvirus; tissues at injection sites were excised at intervals after inoculation and examined under the electron microscope. Electron microscope examination of Yaba virus-induced tumor cells revealed mature and immature virus particles and virus-associated structures such as granular inclusions, cylindrical structures, arch structures, and small spherical membrane structures (micelles). Many micelles were near the granular inclusions and were especially abundant adjacent to the ends of arch structures; arch structures represented an incomplete form of circular, immature virus particle. Micelles were scarce near the virus particles, which were completely circular. Furthermore, micelles were sometimes connected with the inner unit membrane of the arch structures. The micelles were about 400 Å in diameter, with a unit membrane of about 70 Å thick. These observations were thought to indicate a stage in the formation of immature virus particles and

suggested a process of formation by the addition of micelles to the edge of the incomplete hemispheric virus shell membrane. Concurrent assembly of micelles and surface subunits apparently was necessary to regulate a constant curvature of virus particles.

- 0688 REVERSE TRANSCRIPTASE IN TYPE C VIRUS PARTICLES OF HUMAN ORIGIN. (E.) Gallo, R. C. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), P. S. Sarin, P. T. Allen, W. A. Newton, E. S. Priori, J. M. Bowen and L. Dmochowski. *Nature New Biology* 232(31):140-142, 1971.

The presence of RNA-dependent DNA polymerase was reported in type C virus particles from a line of human cells established from pleural effusion cells from an American child with Burkitt's lymphoma (American type). These cells (designated ESP-1 cells) showed an aneuploid karyotype. The virus particles in the ESP-1 cells did not contain the gs antigen of mouse, rat, hamster or cat type C viruses, but did contain the mammalian gs 3 antigen. The finding that ESP-1 cells contained RNA-dependent DNA polymerase was established by the observation of the following features: (1.) an endogenous ribonuclease-sensitive DNA polymerase activity; (2.) a requirement for all 4 deoxynucleoside triphosphates; (3.) dependence on  $Mg^{2+}$ ; (4.) marked enhancement of ESP-1 DNA polymerase activity with RNA extracted from a feline leukemia virus. The exogenous synthetic RNA-DNA hybrid poly dT.rA also enhanced the DNA polymerase reaction in ESP-1 cells, showing that the ESP-1 cell DNA polymerase could utilize both endogenous and exogenous RNA as a template for DNA synthesis.

- 0689 THE PRESENCE OF C-TYPE RNA VIRUS PARTICLES IN A RAT EMBRYO CELL LINE SPONTANEOUSLY TRANSFORMED IN TISSUE CULTURE. (E.) Gazzolo, L. (Internatl. Agency Res. Cancer, Lyons, France), D. Simkovic and M. C. Martin-Berthelon. *J Gen Virol* 12:303-311, 1971.

A line of spontaneously-transformed rat embryo cells (WERC) and a line of WERC cells transformed by Rous sarcoma virus, Prague strain (TWERC), were examined by electron microscope for the presence of virus particles. WERC cells cultured for 4 yr or less were not oncogenic in newborn rats; however, WERC cells cultivated for 4 or more years produced s.c. tumors at the site of inoculation when injected into rats. TWERC cells were more oncogenic in rats than WERC cells. Under the electron microscope, WERC cells appeared fibroblastic while TWERC cells appeared epithelial. Numerous C-type virus particles were seen budding from the plasma membrane in WERC cells; some particles had electron-lucent nu-

cleoids and others had electron-dense nucleoids. About 60-100 virus particles were observed/WERC cell; particles included mature and immature budding C-type particles. Virus particles with electron-dense nucleoids from WERC cells resembled mature murine leukemia virus; the buoyant density of these particles in sucrose gradients was that expected for avian or murine RNA virus particles. No virus particles were seen in TWERC cells.

0690 ASSOCIATION OF 4S RIBONUCLEIC ACID WITH ONCORNAVIRUS RIBONUCLEIC ACIDS. (E.)

Erikson, E. (U. Colorado Med. Ctr., Denver) and R. L. Erikson. *J Virol* 8(2):254-256, 1971.

RNA from oncornaviruses, including avian myeloblastosis virus, Schmidt-Ruppin virus, murine sarcoma virus and murine leukemia virus, was subjected to sucrose gradient centrifugation in order to separate high molecular wt (i.e., 60-70S) from low molecular wt RNA. When avian myeloblastosis virus 65S RNA was heated to 70° C it released a 4S RNA termed 65S-associated RNA. A similar 4S RNA was released from heat-dissociated Schmidt-Ruppin, murine sarcoma and murine leukemia virus RNA. The 65S-associated 4S RNA represented 2.5-3.0% of the RNA in the 65S aggregate of avian myeloblastosis virus RNA. The findings suggested that the 65S RNA aggregate from avian myeloblastosis virus contained transfer-like RNA molecules which were not released until the viral RNA was converted into a 35S form.

0691 TRANSFORMATION OF HUMAN CELLS BY VIRUS AND CHEMICAL CARCINOGEN *IN VITRO*. (E.)

Sekiya, S. (Sch. Med., Chiba U., Japan). *Cancer* 28(3):789-797, 1971.

Cultures of human embryo cells and of human uterine myoma cells were infected with Schmidt-Ruppin Rous sarcoma virus (SR-RSV); alternately, embryo cells were infected with virus and treated with 5 µg/ml of 3-methylcholanthrene (MC); morphological transformation was seen 3-4 wk after infection in embryo cultures. Vacuolated or granulated cells appeared in transformed embryo cell cultures after transformation; in successive embryo cell subcultures vacuolated cells decreased and refractile spindle cells grew during the *in vitro* lifetime. The morphology of embryo cells transformed with SR-RSV alone did not differ from that of cells transformed by SR-RSV and MC. However, the growth pattern of cells treated with virus and MC was more highly irregular than that of cells treated with virus alone. Although infectious virus could not be detected in transformed cultures of human embryo cells, the RSV genome could be detected by inoculation of SR-RSV-infected embryo cells into chicken wing web. To test for transplantability of transformed human cells, cells were in-

jected into cortisone-treated hamsters. Cultures of embryo cells transformed with SR-RSV alone failed to induce tumors in recipient hamsters. However, embryo cells transformed by SR-RSV and MC induced tumors having the histological appearance of fibrosarcomas. A stable line of SR-RSV and/or MC-transformed human embryo or myoma cells could not be established *in vitro*.

0692 CARR-ZILBER STRAIN VIRUS-INDUCED ROUS SARCOMAS IN ADULT MACACA MULATTA: CYTOGENETIC STUDIES. (Rus.) Dzhemilev, Z. A. (U.S.S.R. Acad. Sci., Sukhumi), M. G. Machavariani, F. I. Adzhigitov, I. B. Obukh and D. A. Gubeladze. *Bull Eksp Biol Med* 71(6):74-77, 1971.

Cytogenetic investigations of Rous sarcoma cells were carried out. Rous sarcoma was induced in 2 Macaca mulata monkeys (2½-3 yr-of-age) upon inoculation with a Carr-Zilber strain of Rous sarcoma virus. One monkey had sarcoma in the dorsal region and the other developed sarcoma in the right hip. Tissue samples were taken from tumors after 31 days and 42 days of growth resp. Bone marrow tissue was used as control tissue. The sarcomatous cells elicited a normal karyotype (2n=42) which appeared to be characteristic for the given monkey species. Approximately 90-96% of the cells appeared to be euploid in both tumor and control tissues. Polyploidy occurred in 2.5% of the tumor cells and in 0.9% of the control cells. Aberrant metaphases occurred in 18% of the tumor cells and in 0.4% of the control cells. Abortive mitoses, whereby the chromosomes were at the metaphasic stage and elicited pyknosis, assuming a spherical shape, were seen in 40% of the dividing cells of the sarcomatous tissue. The growth of the tumor may, possibly, depend on the ratio between abortive and nonabortive mitoses.

0693 EPSTEIN-BARR VIRUS IN HUMAN LYMPHOBLASTOID CELLS: ENHANCING THE PERCENTAGE OF VIRUS-POSITIVE CELLS BY COCULTIVATION WITH AFRICAN GREEN MONKEY (VERO) CELLS. (E.) Hampar, B. (Natl. Cancer Inst., Bethesda, Md.), L. M. Martos and J. L. Walker. *J Nat Cancer Inst* 47(3):535-537, 1971.

A line of Burkitt's lymphoma cells (P3HR-1) was cultivated with African green monkey (vero) cells in stationary cultures and unattached P3HR-1 cells were harvested and examined under the electron microscope for Epstein-Barr virus (EBV). By 5-9 days after seeding, the number of unattached P3HR-1 represented approximately 50% of total P3HR-1 cells in cultures. Within the first few days after seeding, the EBV-positive P3HR-1 cells ranged from 10-15% but this progressively increased to reach levels of 60-70% by 10-12 days. The cocultivation procedure for obtaining EBV-positive cells was thought to be especially useful for immunofluorescent and electron microscopic studies.



- 0694 STUDIES OF THE EB VIRUS-RELATED ANTIGENS OF HUMAN LEUKOCYTE CELL LINES. (E.) Walters, M. K. (Queensland Inst. Med. Res., Brisbane, Australia) and J. H. Pope. *Int J Cancer* 8:32-40, 1971.

Complement-fixing (CF) antigens of 5 human leukocyte cell lines were examined; the leukocyte lines studied were QIMR-WIL (from patients with myeloblastic leukemia), QIMR-GOR (from Burkitt's lymphoma patients), TFT-1 (fetal thymic leukocytes transformed by Epstein-Barr virus from QIMR-WIL cells), and RAJI (from Burkitt's lymphoma patients). QIMR-WIL and QIMR-GOR contained Epstein-Barr virus, as did QIMR-STE and TFT-1 cells; RAJI cells were negative for Epstein-Barr virus. When heated for 30 min at 56° C, all cell lines except RAJI showed some reduction in CF antigen titer, a portion of the CF activity remaining; RAJI antigen showed no loss in titer when exposed to heat. The antigens of all cell lines except RAJI showed a 2-4-fold reduction in CF titer when centrifuged at 70,000 x g for 2 hr. Three CF-antigen components were recognized in the Epstein-Barr virus-rich QIMR-WIL line; (1.) a virion component harvested from sucrose density gradients and resistant to heating at 56° C for 30 min; (2.) a heat-labile CF component which was subviral and which was sedimentable at 70,000 x g for 2 hr; (3.) a heat-resistant soluble CF antigen. The soluble portions of antigens prepared from each of the 5 cell lines were studied by equilibrium density gradient centrifugation. The soluble antigens of the cell lines other than RAJI were relatively homogeneous with regard to molecular size, while those of RAJI showed greater heterogeneity. Evidence obtained suggested that naked virus was capable of transforming human leukocytes.

- 0695 C-TYPE TUMOR VIRUS PARTICLES IN SALIVARY TISSUE OF DOMESTIC CATS. (E.) Gardner, M. B. (U. Southern California Sch. Med., Los Angeles), R. W. Rongey, E. Y. Johnson, R. DeJournett and R. J. Huebner. *J Nat Cancer Inst* 47(3):561-565, 1971.

Submaxillary and parotid salivary gland tissue from domestic cats with various malignant and nonmalignant conditions was examined under the electron microscope. Sample material included cats with spontaneous lymphoma, spontaneous carcinoma, infectious peritonitis, experimental feline sarcoma virus infection, and normal cats. C-type RNA virus particles were found in the submaxillary gland of 13 of 14 cats with spontaneous lymphoma, in 8 of 9 cats with feline sarcoma virus-induced sarcoma, and in 2 of 4 cats with severe anemia. Particles were less frequent in the submaxillary gland of cats with spontaneous sarcoma (1/5) or infectious peritonitis (1/5), and were not seen in 10 cats with carcinoma or in 6 normal cats. C-type particles were present in unusually large numbers in salivary tissue of lymphomatous cats; particles were found especially around the base of the acinar cells and within acinar lumina. Particles were numerous in saliva of a kitten with a feline sarcoma virus-induced sarcoma. Virus particles

were not seen in association with either interstitial fibroblasts or capillary endothelial cells. Most particles resembled the "immature" C-type, being about 100 mμ in diameter. There were usually more C-type particles in the submaxillary glands than in the parotid glands. Each cat with lymphoma, sarcoma, unexplained anemia or infectious peritonitis and with C-type particles in the salivary glands also had identical particles in the bone marrow. However, C-type particles were seen in the bone marrow but not in the salivary tissue of 1 cat with carcinoma and 2 cats with infectious peritonitis.

- 0696 FERRITIN-LABELED ANTIBODY STUDIES OF FELINE C-TYPE PARTICLES. (E.) Oshiro, L. S. (California State Dept. Publ. Hlth., Berkeley), J. L. Riggs, D. O. N. Taylor, E. H. Lennette and R. J. Huebner. *Cancer Res* 31(8):1100-1110, 1971.

Cell lines established from cats with lymphoma, leukemia or idiopathic agranulocytosis were covered with dog anti-feline sarcoma serum and with ferritin-labeled rabbit anti-dog conjugate prepared by immunizing rabbits with canine γ-globulin. The cat cell lines contained the feline C-type virus particle. Dog anti-feline sarcoma serum was obtained from a 1-yr-old female beagle inoculated with a tissue homogenate from a tumor induced by inoculation of feline sarcoma virus into her puppies. A feline anti-feline sarcoma serum was also used. Canine and feline anti-feline sarcoma virus sera were found to have specific activity against feline C-type virus particles and infection-mediated cell surface antigens as determined by indirect ferritin-labeled antibody tagging. Ferritin tagging of viruses and cell membranes was similar in the 6 feline cell lines observed. Evidently the lines shared antigen components. To exclude the possibility that the membrane tagging was due to altered surface antigens common to malignant cells having nothing to do with virus production, normal feline cells were infected *in vitro* and tested for ferritin-labeled antibody tagging. The viral and membrane tagging were similar to those observed in lines established from affected host tissues. Each instance of ferritin-labeled antibody tagging previously had been shown to be positive with fluorescent antibody staining, showing that there was a correlation between fluorescent antibody staining of feline C-type virus-producing cells and ferritin tagging of the virus and infection-mediated membrane antigens.

- 0697 MECHANISM OF CARCINOGENESIS BY RNA TUMOUR VIRUSES: THE RNA- AND DNA-DEPENDENT DNA POLYMERASE ACTIVITIES OF FELINE SARCOMA VIRUS. (E.) Fujinaga, K. (St. Louis U. Sch. Med., Mo.) and M. Green. *J Gen Virol* 12:85-93, 1971.

In a study of the DNA polymerase activities of a feline sarcoma virus (FSV) it was found that the FSV DNA polymerase reaction required treatment with detergent. The kinetics of DNA synthesis by the FSV polymerase showed a biphasic pattern consisting of an initial rapid reaction for about 4 min followed by a second slower reaction which reached a plateau in 20-60 min. The [ $^3\text{H}$ ]DNA product synthesized by FSV in the absence of added template was purified and analyzed by equilibrium centrifugation in  $\text{Cs}_2\text{SO}_4$  density gradients. [ $^3\text{H}$ ]DNA synthesized during the first 12 sec. banded at a density close to that of RNA implying the formation of virus RNA-[ $^3\text{H}$ ]DNA complexes composed of virus RNA with small amounts of DNA. Some of the 12 sec. DNA product, and virtually all of the DNA formed by 4 min and later, banded at the density of uncompleted DNA, free of a virus RNA template. About half of the 60 min DNA product was double-stranded, as indicated by its resistance to digestion by exonuclease I and by its elution from hydroxyapatite columns at the salt concentration characteristic of duplex DNA.  $\text{CsCl}$  equilibrium sedimentation of alkali-denatured, 15, 30 and 60 min FSV [ $^3\text{H}$ ]DNA products in  $\text{CsCl}$  density gradients showed a broad distribution of [ $^3\text{H}$ ]DNA with mean buoyant densities of 1.724, 1.725 and 1.725, resp. These DNA products sedimented at 6S. Calf thymus DNA stimulated DNA polymerase activity of detergent-treated virus particles by 10-20-fold, indicating that the virus particles harbored DNA-dependent as well as RNA-dependent DNA polymerase activity.

0698 RESISTANCE OF AKR MICE TO LYMPHOID LEUKEMIA ASSOCIATED WITH A CHRONIC PROTOZOAN INFECTION, *Besnoitia jellisoni*. (E.) Lunde, M. N. (Natl. Inst. Allergy Infec. Dis., Bethesda, Md.) and A. H. Gelderman. *J Nat Cancer Inst* 47(2):485-488, 1971.

The effect of infection with *Besnoitia jellisoni*, a toxoplasma-like murine parasitic protozoan, on the incidence of spontaneously-arising leukemia was investigated in AKR and in Swiss-Webster mice. AKR mice are congenitally infected with Gross strain A leukemia virus and have a high incidence of spontaneous leukemia; Swiss-Webster mice have a low incidence of spontaneous leukemia. AKR mice infected with *B. jellisoni* had a lower leukemia mortality than uninfected AKR mice; by 250 days after birth, approximately 55% of uninfected mice had died of leukemia and 7% of infected mice had died of leukemia. By age 12 months, 90% of uninfected mice had died of leukemia and 15% of infected mice had died of leukemia. AKR mice were resistant to acute *B. jellisoni* infection; 18-21 days after inoculation of trophozoites, 42% of Swiss-Webster mice had died, while none of the AKR mice similarly infected had died at this time. It was thought that the apparent resistance to leukemia associated with *B. jellisoni* infection in AKR mice was due to activation of macrophages by the protozoan.

0699 MURINE LEUKAEMIA VIRUS GROUP-SPECIFIC ANTIGEN IN THE C-TYPE VIRUS-CONTAINING HUMAN CELL LINE, ESP-1. (E.) Gilden, R. V. (Flow Labs., Inc., Rockville, Md.), W. P. Parks, R. J. Huebner and G. J. Todaro. *Nature* 233(5315):102-103, 1971.

The immunological relationship between the C-type virus in human ESP-1 cells and the known mammalian C-type viruses was explored in complement-fixation (CF), radioimmunoprecipitin inhibition and gel diffusion studies. The ESP-1 cell line was derived from a patient with lymphoma. The C-type virus particle in ESP-1 cells appeared to be a murine virus. The following reagents gave consistent positive reactions in CF tests with ESP-1 cell homogenates: (1) 8 serum pools from rats bearing murine sarcoma virus-induced tumors (serum pools were selected for reactivity to the mouse gs antigen); (2) serum from 2 rabbits and 3 guinea-pigs immunized with the purified gs antigen of mouse C-type viruses (murine leukemia virus). No CF reactivity was obtained with guinea-pig antiserum prepared against purified feline, rat, or hamster leukemia virus gs antigen. The regularity with which positive reactions were obtained at different cell passage levels, with different sources of anti-murine gs sera, and in different laboratories, strongly suggested cross-reactivity in ESP-1 cells with murine leukemia virus gs antigens. Equally important in indicating specificity for murine leukemia virus was the absence of reactivity in CF tests with ESP-1 cell extracts and antisera which detect feline and hamster gs antigens. Further evidence that the ESP-1 antigen was cross-reactive with murine leukemia gs antigen was obtained by radioimmunoprecipitin inhibition tests and immunodiffusion tests.

0700 THE IMMUNOSUPPRESSIVE EFFECTS OF RAUSCHER LEUKEMIA VIRUS UPON SPLEEN CELLS CULTURED IN CELL-IMPERMEABLE DIFFUSION CHAMBERS: II. EFFECTS UPON IgM AND IgG IMMUNOLOGIC MEMORY AND ON RESPONSE TO PHYTOHEMAGGLUTININ AND STIMULATION WITH ALLOGENEIC CELLS. (E.) Borella, L. (U. Tennessee Med. Unit, Memphis). *J Immunol* 107(2):464-475, 1971.

Experiments were designed to determine, in cell-impermeable diffusion chambers, the effects of Rauscher leukemia virus (RLV) on the cellular expression of IgM and IgG memories and on cell responses to phytohemagglutinin (PHA) and allogeneic stimulation; BALB/c mouse spleen cells were used. Spleen cells from mice which had been primed 2 or 45 days earlier with sheep red blood cells (SRBC) were cultured with or without SRBC; half the cultures were inoculated with RLV. RLV inoculated at time zero of culture did not depress SRBC-IgM memory; the initiation of the IgM response, the slope of the log phase, and the peak value of IgM plaque-forming cell (PFC) production were similar in RLV-inoculated and in uninoculated cultures. On the other hand, IgG memory was depressed by RLV inoculation; the peak of IgG PFC



response in inoculated cultures was less than 10% of its value in controls. Both IgM and IgG responses were depressed when the interval between RLV inoculation and antigenic restimulation was increased. Removal of the macrophage-rich, glass-adherent cells from spleen cell cultures depressed the IgM but not the IgG response. This indicated that the suppression of IgG memory by RLV was not related to an effect on the adherent macrophage-rich cell population. Incorporation of  $^3\text{H}$ -TdR was higher in spleen cell cultures infected with RLV than in non-infected controls. Stimulation of  $^3\text{H}$ -TdR incorporation by PHA was demonstrated in cultures of spleen cells from mice inoculated with RLV; the cpm recorded in cultures of RLV-infected cells incubated with PHA were similar to those in PHA-stimulated uninfected cultures. Findings suggested that the RLV-induced immunosuppression is not an all-or-none phenomenon, and that there are quantitative and qualitative differences in the effect of RLV on various components of the immune system.

(St. Louis U. Sch. Med., Mo.) and M. Green. *J Molec Biol* 60:185-202, 1971.

The properties of adenovirus DNA-polyribonucleotide complexes and the separation of the intact, complementary viral DNA strands by centrifugation were described. Single-stranded viral DNA was prepared from purified adenovirus types 2, 7 and 12 by heating to 100° C or by treatment with phenol-alkali; viral DNA isolated by either method was equally effective in binding to poly(U,G), and DNA isolated by either method formed 2 DNA-poly(U,G) bands in CsCl density gradients. The ability of poly(A), poly(C), poly(G) and poly(U) to bind denatured adenovirus 2 DNA was tested. At pH 7.2 only poly(G) and poly(U) were bound to adenovirus 2 DNA in quantities sufficient to increase the density of denatured DNA. At pH 5.0 the density of denatured adenovirus 2 was increased by poly(C) and slightly increased by poly(A). Complex formation with poly(A), poly(C) or poly(U) did not result in the separation of adenovirus 2 strands. Poly(U,G) preparations, with suitable ratios of U:G bound to both strands of viral DNA and produced increases in buoyant density of 50-80 mg/cm<sup>3</sup>. Adenovirus 2, 7 and 12 DNA behaved differently in their binding of poly(U,G) preparations. Since viral DNA strands showed different buoyant densities, heavy and light DNA strands could be separated as intact DNA molecules sedimenting at 35S; in the case of adenovirus 2 DNA it was found that each strand was relatively pure and uncontaminated by material from its sister DNA strand.

0701 RNA DEPENDENT DNA POLYMERASE IN C TYPE PARTICLES FROM NORMAL RAT THYMUS CULTURES.

(E.) Teitz, Y. (Tel-Aviv U. Med. Sch., Israel). *Nature New Biology* 232(34):250-252, 1971.

C-type virus particles from normal and Moloney leukemia virus-infected rat thymus cell cultures were purified and C-type particles from sucrose gradients at a density of about 1.14-1.18 g/ml were assayed for RNA dependent DNA polymerase activity. The requirements and degree of incorporation of  $^3\text{H}$ -TMP by C-type particles from normal rat thymus cultures were similar to those shown by the Moloney leukemia virus grown in rat thymus cultures. Addition of detergents such as "Nonidet P-40," "Tween" 20, 40 or 80 or "Triton X-100" markedly increased the incorporation of  $^3\text{H}$ -TTP by both Moloney leukemia virus C-type particles and the "normal" C-type particles. The inhibitory effect of rifamycin on  $^3\text{H}$ -TTP incorporation by C-type particles was similar in Moloney leukemia virus C-type particles and "normal" C-type particles. There was, however, a difference in the inhibitory effect of actinomycin D on incorporation from  $^3\text{H}$ -TTP between Moloney leukemia virus and the "normal" C-type particles; while 0.5 µg actinomycin inhibited 50% of the incorporation of  $^3\text{H}$ -TMP by Moloney leukemia virus particles, 5 µg actinomycin caused a 50% reduction in the incorporation by the C-type particles from the normal rat thymus cultures. The difference in response to actinomycin may indicate that the DNA polymerase of Moloney leukemia virus can be distinguished from that of the "normal" C-type particles.

0703 INDUCTION OF HEPATOMAS IN HAMSTERS BY AN AVIAN ADENOVIRUS (CELO). (E.) Anderson,

J. P. (Baylor Coll. Med., Houston, Texas), K. J. McCormick, W. A. Stenback and J. J. Trentin. *Proc Soc Exp Biol Med* 137(2):421-423, 1971.

Inbred strain LSH/LAK hamsters and random bred hamsters were inoculated s.c. with Phelps strain chick embryo lethal orphan virus (CELO), an avian adenovirus; virus inocula ranged in size from 10<sup>6.6</sup> to 10<sup>7.9</sup> TCID<sub>50</sub>. Random bred hamsters developed tumors in 67-91% of cases; the 91% tumor incidence was seen in animals given 10<sup>7.9</sup> TCID<sub>50</sub> doses of virus. Inbred hamsters developed tumors in 33-82% of cases; the 82% tumor incidence was seen in animals given 10<sup>6.6</sup> TCID<sub>50</sub> doses of virus. Most of the tumors were found at the site of inoculation and were diagnosed histologically as fibrosarcomas. About 4% of inbred hamsters developed hepatomas. Sera from hepatoma-bearing hamsters stained the CELO tumor antigen found in lytically infected chick kidney cells. The hepatomas induced in hamsters by CELO virus contained hamster types A and C virus particles.

0702 ADENOVIRUS DNA: III. SEPARATION OF THE COMPLEMENTARY STRANDS OF ADENOVIRUS TYPES 2, 7 AND 12 DNA MOLECULES. (E.) Landgraf-Leurs, M.

0704 ADENOVIRUS ENDONUCLEASE: ASSOCIATION WITH THE PENTON OF ADENOVIRUS TYPE 2. (E.)

Burlingham, B. T. (Rockefeller U., New York, N.Y.),

W. Doerfler, U. Pettersson and L. Philipson.  
*J Molec Biol* 60:45-64, 1971.

Capsomeres purified from adenovirus type 2 (Ad2) were assayed for endonuclease activity; the Ad2 was taken from infected KB cells. Hexon, penton and fiber were purified from KB cells infected with Ad2; each subunit was assayed for endonuclease activity. Only the penton, consisting of penton base and fiber, had endonuclease activity. Hexon and fiber did not hydrolyze DNA. Since purified fiber alone did not hydrolyze DNA, it was thought that the penton base probably contained the endonuclease activity. When the penton was digested with dilute trypsin, endonuclease activity was destroyed. In partially purified preparations of penton, the amount of endonuclease activity correlated with the amount of penton base antigen and not with the amount of total protein. The degree of competition between fiber or hexon and the penton endonuclease for the viral DNA was determined; no competition was found. Antiserum against Ad2 completely inhibited the endonuclease activity of the penton from Ad2, but antiserum against Ad type 12 had no effect on Ad2 penton endonuclease. Evidently, the endonucleases of Ad2 and Ad12 are antigenically different, though both viruses were grown in the same KB cell line. When the substrate specificity of the Ad2 penton endonuclease was investigated, it was found that the endonuclease had specific sites of attack which appeared to coincide on the adenovirus molecule with regions rich in guanine and cytosine bases. The penton endonuclease was specific for DNA and hydrolyzed native DNA at 20 times the rate at which it hydrolyzed denatured DNA.

0705 CUTANEOUS SKIN TEST FOR DELAYED HYPERSENSITIVITY IN HAMSTERS TO VIRAL INDUCED TUMOR ANTIGENS. (E.) Olsen, R. G. (Dept. Veterinary Path., Ohio State U., Columbus), J. R. McCammon, J. Weber and D. S. Yohn. *Canad J Microbiol* 17(8):1145-1147, 1971.

The delayed-type hypersensitivity immune response to DNA and RNA virus-induced tumor antigens was monitored in hamsters. Skin tests for hypersensitivity were performed with virus-induced tumor antigens on hamsters bearing tumors induced by adenovirus 12 (Ad-12), Schmidt-Ruppin strain Rous sarcoma virus (RSV-SR), SV40 virus or SV40 virus DNA. Antigens prepared from tumors induced by these viruses were administered intradermally to hamsters in amounts of 0.05 ml. Of 39 Ad-12 tumor-bearing hamsters, 36 reacted to Ad-12 tumor antigen and none reacted to SV40 tumor antigen; 1 of 16 Ad-12 tumor-bearing animals reacted with RSV-SR tumor antigen. Of 77 hamsters with RSV-SR-induced tumors 60 gave a positive delayed-type skin test to RSV-SR tumor antigen and 1 reacted with Ad-12 tumor antigen. Skin tests on tumor-free hamsters showed no reaction with Ad-12 tumor antigens in 25 animals and no reaction with SV40 tumor antigens in 10 animals tested. Ad-12 and RSV-SR tumor

bearing hamsters developed positive delayed-type skin test to homologous antigen at the time tumors in the hamsters became palpable.

0706 BIOCHEMICAL STUDIES ON ADENOVIRUS MULTIPLICATION: XIX. RESOLUTION OF LATE VIRAL RNA SPECIES IN THE NUCLEUS AND CYTOPLASM. (E.) Parsons, J. T. (Inst. for Molec. Biol., U. Zurich, Switzerland), J. Gardner and M. Green. *Proc Nat Acad Sci USA* 68(3):557-560, 1971.

Human KB cells were infected with adenovirus 2 and labeled with  $^3\text{H}$ -uridine for 15 and 60 min; late nuclear RNA species were resolved by electrophoresis on polyacrilamide gels 18 hr after virus infection. As many as 10 virus-specific RNA species larger than 26S could be detected after 15 and 60 min labeling periods; these 10 RNAs had sedimentation coefficients of 26S-43S and ranged in molecular weight from  $1.4 \times 10^6$  to  $4.3 \times 10^6$ . Viral RNAs with sedimentation coefficients of 36S, 38S, 40S and 43S were synthesized predominantly during a 15 min labeling period with  $^3\text{H}$ -uridine. Smaller RNAs accumulated when labeling was continued for longer periods. Six to eight species of viral RNA were found in virus-infected cell cytoplasm; these RNAs had sedimentation coefficients ranging from 10S-29S and molecular weights ranging from  $0.19 \times 10^6$  to  $1.82 \times 10^6$ . It was thought that these RNAs were stable, functional viral messenger RNAs transcribed late after virus infection. DNA-RNA hybridization-competition experiments indicated that all of the high molecular weight nuclear RNA species in the virus-infected cells were present in both cytoplasmic and polyribosomal RNA; these nuclear RNAs were thought to represent precursors to some of the cytoplasmic viral RNAs.

0707 STUDIES OF NONDEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES: IV. CHARACTERIZATION OF THE SIMIAN VIRUS 40 RIBONUCLEIC ACID SPECIES INDUCED BY WILD TYPE SIMIAN VIRUS 40 AND BY NONDEFECTIVE HYBRID VIRUS Ad2<sup>+</sup>ND<sub>1</sub>. (E.) Oxman, M. N. (Harvard Med. Sch., Boston, Mass.), A. S. Levine, C. S. Crumpacker, M. J. Levin, P. H. Henry and A. M. Lewis, Jr. *J Virol* 8(2):215-224, 1971.

The relationship of the SV40-specific RNA sequences transcribed from the Ad<sup>+</sup>ND<sub>1</sub> DNA to those transcribed from the DNA of SV40 itself was investigated; Ad2 ND<sub>1</sub> is a non-defective adenovirus 2-SV40 hybrid virus which contains a small segment of the SV40 genome covalently linked to adenovirus 2 DNA. In hybridization-competition experiments, unlabeled late SV40 RNA competed efficiently (> 90%) with late SV40  $^3\text{H}$ -RNA. Hybridization competition of unlabeled Ad2<sup>+</sup>ND<sub>1</sub> RNA with Ad2ND<sub>1</sub>  $^3\text{H}$ -RNA revealed complete competition. Furthermore, both early and late SV40 RNA competed 85% or more with the Ad2<sup>+</sup>ND<sub>1</sub>  $^3\text{H}$ -RNA. A comparison of the slopes of the competition curves obtained with early and late



SV40 RNA species suggested that the SV40-specific sequences in Ad2<sup>+</sup>ND<sub>1</sub> <sup>3</sup>H-RNA were present in much higher concentrations in the late SV40 RNA competitor than in the early SV40 RNA competitor. When unlabeled Ad2<sup>+</sup>ND<sub>1</sub> RNA was used as a competitor, Ad2<sup>+</sup>ND<sub>1</sub> RNA competed with 40% of early SV40 <sup>3</sup>H-RNA while Ad2<sup>+</sup>ND<sub>1</sub> RNA competed with only 15% of late SV40 <sup>3</sup>H-RNA. Further competition experiments confirmed the observation that early SV40 RNA contained most (if not all) of the SV40 nucleotide sequences present in Ad2<sup>+</sup>ND<sub>1</sub> RNA. RNA-DNA hybridization-competition studies indicate that the SV40 component of Ad2<sup>+</sup>ND<sub>1</sub> consists of some, but not all, of that part of the SV40 genome which is transcribed early, i.e., prior to viral DNA replication, in SV40 lytic infection.

with SV40 after Ad 2 infection. Protein synthesis and transport were studied by autoradiography in productively infected HeLa and Vero cells, and in abortively infected GMK cells. In productively infected HeLa and Vero cells most of the viral proteins were synthesized in the cytoplasm and then transferred to the nucleus; 62-70% of grains were found over the nucleus in these infected cells after a 2 hr chase period. In abortively infected GMK cells, however, only 20-28% of the grains were observed in the nucleus after a 2 hr chase period. Evidently, either viral proteins were not synthesized or they were not transported across the nuclear membrane. GMK cells co-infected with SV40 had an increased grain count in the nucleus (49-52%) after the chase period. It was thought that, during Ad 2 abortive infection, a reduction in viral protein synthesis occurred as well as an inhibition of protein transport into the nucleus.

0708 APPLICATION OF AN INDIRECT PAIRED RADIO-  
IODINE-LABELED ANTIBODY TECHNIQUE TO ADENO-  
VIRUS-12 TUMOR SEROLOGY. (E.) McCammon, J. R.  
(Dept. Veterinary Path., Ohio State U., Columbus)  
and D. S. Yohn. *J Nat Cancer Inst* 47(2):447-454,  
1971.

0710 ONCOGENIC TRANSFORMATION OF HAMSTER CELLS  
AFTER EXPOSURE TO HERPES SIMPLEX VIRUS  
TYPE 2. (E.) Duff, R. (Hershey Med. Ctr., Pennsylv-  
ania State U., Hershey) and F. Rapp. *Nature New  
Biology* 233(3B):48-50, 1971.

The indirect paired radioiodine-labeled antibody technique (indirect PRILAT) was evaluated as a means for screening hamster sera for antibodies to the adenovirus-12 (Ad-12) tumor antigen; the sensitivity of PRILAT in detecting antibody was compared with the sensitivities of the indirect immunofluorescence (indirect IF) and with the complement fixation test (CF). Antibody against Ad-12 tumor antigen was obtained from hamsters inoculated with the Ad-12 virus as newborns. Twelve sera from normal control hamsters and 21 sera from primary, Ad-12 tumor-bearing hamsters were titrated from 1:5 through 1:2,560 for Ad-12 tumor antibody by CF, indirect IF and indirect PRILAT. Of the 12 control sera, none were antibody positive at any dilution in the 3 tests. Of the 21 sera from tumor-bearing hamsters, 12 were antibody-negative at 1:5 by CF; of these 12 sera, 11 were antibody-positive by indirect IF and all were positive by indirect PRILAT. All 9 sera positive for antibody by CF were also positive by indirect IF and by PRILAT. Ad-12 antibody titers in CF-negative sera ranged from 1:20-1:160 by indirect IF and from 1:160 to  $\geq$  1:2,560 by indirect PRILAT. Thus, the indirect PRILAT afforded a greater degree of sensitivity for detection of Ad-12 tumor antibody than indirect IF and a markedly greater sensitivity than CF.

Preliminary results demonstrated continued involvement of herpes simplex virus type 2 (HSV-2) in hamster embryo fibroblasts transformed *in vitro* by virus exposed to UV. Hamster cells were exposed to HSV-2 which had been irradiated for up to 8 min from a UV source. Irradiation reduced the infectivity of the virus preparation from  $3 \times 10^6$  to less than 10 plaque-forming U ml<sup>-1</sup>. Foci of morphologically transformed cells appeared 21-28 days after viral exposure, but the frequency of transformation was low, and only 2 of 17 culture bottles contained foci of morphologically transformed cells. A transformed focus was extracted and grown as a cell line (designated 333-8-9). Newborn hamsters were injected with  $5 \times 10^5$  333-8-9 cells; palpable tumors were detected 10-16 wk postinjection. Eleven of 30 injected hamsters developed tumors. No infectious HSV-2 was found in 333-8-9 cells. However, the continued presence of the HSV-2 genome in 333-8-9 cells was detected by the demonstration of herpes specific antigens within the cell line. The cytoplasm of about 1-5% of transformed 333-8-9 cells contained a diffuse antigen. In addition, sera from HSV-2-induced tumor-bearing hamsters were tested for the presence of HSV-neutralizing antibodies and were found to neutralize HSV-2 from 3-10 times more efficiently than HSV-1. Under the same experimental conditions, normal hamster sera did not neutralize HSV-2.

0709 MECHANISM OF HOST CELL RESTRICTION IN  
AFRICAN GREEN MONKEY KIDNEY CELLS ABORTIVE-  
LY INFECTED WITH HUMAN ADENOVIRUS TYPE 2. (E.)  
Henry, C. J. (Allegheny Gen. Hosp., Pittsburgh, Pa.),  
M. Slifkin and L. Merkow. *Nature New Biol* 233(3B):39-  
41, 1971.

0711 DIFFERENTIATION BETWEEN TYPE 1 AND TYPE 2  
STRAINS OF HERPES SIMPLEX VIRUS BY AN IN-  
DIRECT IMMUNOFLOUORESCENT TECHNIQUE. (E.) Geder, L.  
(Med. Sch., Birmingham, England) and G. R. B. Skinner.  
*J Gen Virol* 12:179-182, 1971.

Synthesis and transport of viral specific proteins during abortive adenovirus infection were studied. HeLa, Vero and GMK (monkey) cells were infected with adenovirus type 2 (Ad 2); GMK cells were co-infected

A simple and rapid immunofluorescent method for typing strains of herpes simplex virus was reported. Antisera to herpes simplex virus types 1 and 2 were prepared in rabbits by a prolonged course of immunization with freeze-dried extracts of disrupted infected cells. Sera were absorbed with herpes virus-infected baby hamster kidney cells. Tests for immunofluorescence were made by the indirect method using antiserum to rabbit  $\gamma$ -globulin prepared in sheep; baby hamster kidney cells infected with types 1 and 2 herpes simplex virus were treated with anti-herpes serum. By absorbing anti-herpes sera with cells infected with heterotypic virus strains the sera became type specific for these antigens on the surfaces of cells infected for 5.5 hr. Cell-membrane antigens induced by type 1 herpes simplex virus appeared as very fine granules equally distributed along the cytoplasmic membrane. The cell-membrane antigens induced by type 2 herpes simplex virus appeared as intermittent large granules. These results suggested, and further tests confirmed, that cell-membrane immunofluorescence with absorbed sera would be a reliable means of virus type differentiation. The indirect cell-membrane immunofluorescent test made with "type-specific" antisera established a new method of typing of new herpes simplex virus isolates.

- 0712      HERPES SIMPLEX VIRUS AND CANCER OF THE CERVIX. (E.) Plummer, G. (Loyola U. Med. Sch., Maywood, Ill.) and J. G. Masterson. *Amer J Obstet Gynec* 111(1):81-84, 1971.

A study of the incidence of type 2 herpes simplex virus antibody in Caucasian American women from a relatively high socioeconomic group was performed using neutralization curves and doubling-dilution neutralization tests. Subjects included 27 women with invasive cervical cancer and 47 age-matched controls without cancer. Both tests indicated a higher incidence of type 2 virus antibody among cancer patients than among controls. Based on neutralization curves, 30-48% of patients had specific type 2 antibody while 9-18% of controls had type 2 antibody. Based on doubling-dilution neutralization test results, 30% of sera from patients had type 2 antibody and 13% of controls had type 2 antibody. Four cancer patients and 13 controls had no antibody to either type 1 or type 2 herpes simplex virus. Due to marked cross-neutralization of type 2 by antibody to type 1 virus, results were regarded with caution.

- 0713      DIFFERENCES IN THE PROPERTIES OF THYMIDINE KINASE PRODUCED IN CELLS INFECTED WITH TYPE 1 AND TYPE 2 HERPES VIRUS. (E.) Thouless, M. E. (Dept. Virol., U. Birmingham, England) and G. R. B. Skinner. *J Gen Virol* 12:195-197, 1971.

Baby hamster kidney cells (BHK) were infected with herpes simplex virus types 1 and 2 and thymidine

kinase activity was measured in infected cells; BHK cells infected with herpes simplex virus type 1 produced a rather stable thymidine kinase which could be kept for 1 hr at 40°. By contrast, thymidine kinase produced by BHK cells infected with type 2 herpes simplex virus could not be kept satisfactorily at 40°. Preparations of thymidine kinase from type 2 virus-infected cells did not give a linear dose/activity curve on dilution while type 1 virus-infected cell enzyme did. Furthermore, antiserum against cells infected with type 2 virus did not inactivate either type 1 or type 2 thymidine kinase; antiserum against RK 13 cells infected with type 1 virus did inactivate type 1 thymidine kinase but failed to inactivate type 2 thymidine kinase.

- 0714      REPLICATION OF MAMMARY TUMOR VIRUS IN TUMOR CELL CULTURES: DEPENDENCE ON HORMONE-INDUCED CELLULAR ORGANIZATION. (E.) McGrath, C. M. (Dept. Bacteriol. Immunol., U. California, Berkeley). *J Nat Cancer Inst* 47(2):455-466, 1971.

A study was made to determine the effect of insulin, hydrocortisone and prolactin on mammary tumor virus (MTV) replication in chronically virus-infected mouse mammary epithelium. When cultures of MTV-infected mammary adenocarcinoma cells from BALB/cfC3H female mice were cultivated in media supplemented with 7% fetal calf serum but without hormone, media were virtually inactive in the *de novo* production of MTV. Adding insulin resulted in release of MTV; maximum induction, usually a 10-15-fold increase over MTV production in non-insulin-treated cultures, required 10  $\mu$ g/ml of insulin. Maximum release of MTV virions occurred between 36-48 hr after addition of insulin. Recovery of MTV from insulin-treated cultures was correlated with the appearance of 3-dimensional cellular structures ("domes"). The epithelioid cells confined to these domes were the primary foci of MTV production. Hydrocortisone stimulated MTV production in BALB/cfC3H cells; MTV production increased maximally between 12-24 hr after addition of hydrocortisone. Domes were also associated with MTV release in hydrocortisone-treated cultures. Stimulation of MTV production and dome development by hydrocortisone required pretreatment of tumor cells with insulin. Hydrocortisone acted without mitogenic stimulation of cells and did not modify kinetics of MTV replication per infected cell. Prolactin did not measurably influence MTV production.

- 0715      *IN VITRO* RELATIONSHIP OF SV40 TUMOUR-SPECIFIC SURFACE ANTIGEN TO OTHER SV40 ANTIGENS. (E.) Wright, P. W. (Natl. Cancer Inst., Bethesda, Md.). *Nature New Biology* 233(35):18-19, 1971.

The relationships between a tumor-specific surface (TSS) antigen expressed by SV40-transformed mouse



cells and the virus-specific surface (S) antigen associated with SV40-transformed hamster cells was investigated. Four embryonic hamster cell lines were used: line 1808, transformed by SV40 and containing both SV40 tumor (T) and S antigens (T+S+); line 2952, a clone established from 1808 and containing T and S antigens (T+S+); line 1807, transformed by SV40 and containing only the S antigen (T-S+); and line 1809, spontaneously transformed and lacking both T and S antigens (T-S-). Cells from the 4 lines were incubated with antiserum to the TSS antigen; antiserum was obtained from an SV40-transformed mouse cell line designated SV.AL/N. Only the 2 T+S+ cell lines (1808 and 2952) were sensitive to anti-SV.AL/N antiserum; the other 2 cell lines, including the 1807 cell line which contained the S antigen, were unreactive. These observations were supported by quantitative absorption experiments. Aliquots of anti-SV.AL/N serum were combined with cells from the 4 hamster cell lines and incubated for 60 min. at 37°C. Cell mixtures were centrifuged (2,000 g) for 5 min. and the supernatant serum was removed and tested for residual cytotoxic activity against labeled SV.AL/N mouse target cells. Only the 2 T+S+ cell lines efficiently reduced the activity of the anti-SV.AL/N serum. The results suggested that the TSS antigen was shared by both the 2 SV40 T+S+ hamster cell lines. Since the TSS antigen was not detected on T-S+ (i.e., 1807) cells, it was presumably not identical to the S antigen.

0716 CONTACT-INHIBITED REVERTANT CELL LINES ISOLATED FROM SV40-TRANSFORMED CELLS: I. BIOLOGIC, VIROLOGIC AND CHEMICAL PROPERTIES. (E.) Culp, L. A. (Harvard Med. Sch., Boston, Mass.), W. J. Grimes and P. H. Black. *J Cell Biol* 50:682-690, 1971.

SV40-transformed mouse 3T3 cells (SV-3T3) were exposed to 5-fluoro-2'-deoxyuridine to isolate contact-inhibited "revertant" cell lines. Two revertant clones were established; revertant cells resembled 3T3 cells morphologically in that both 3T3 and revertant lines contained cells which were large, pleomorphic and polygonal or epithelioid in morphology. Many multi-nucleated giant cells were seen in revertant cultures; giant cells were less common in SV-3T3 cells. SV40 T antigen was detected by fluorescent antibody tests in almost all nuclei of revertant cells, and SV40 could be rescued from revertants by fusion with permissive monkey cells. Transformation frequencies in 3T3 cells exposed to SV40 from revertant cell lines were similar to those in 3T3 cells exposed to wild-type SV40. Revertant cells contained more sialic acid than SV-3T3 cells; the 2 revertant cell lines contained 4.4 and 4.8 µg sialic acid/mg protein, resp., whereas SV-3T3 cells contained 3.0 µg sialic acid/mg protein. An inverse correlation was found between the saturation density of cells and their sialic acid content. Collagen content was similar in revertant and SV-3T3 cells. Contact inhibition of revertant cells may be related to sialic acid content of the cell plasma membrane.

0717 INTERRUPTION OF SV40 ONCOGENESIS WITH HUMAN FOETAL ANTIGEN. (E.) Ambrose, K. R. (Oak Ridge Natl. Lab., Tenn.), N. G. Anderson and J. H. Coggin. *Nature* 233(5316):194-195, 1971.

Cross immunization of adult hamsters against SV40 virus tumorigenesis by human fetal cell homogenates was reported. SV40 virus was used to infect newborn hamsters. Infected hamsters were immunized with 3 injections of 1 of the following: SV40, irradiated SV40 hamster tumor cells, human embryo kidney cells, adult kidney cells, lyophilized SV40 tumor cells or 10-day gestation hamster fetal cells. By 56-60 days after SV40 infection, non-immunized SV40-infected hamsters showed significant levels of cytostatic antibody (C-antibody). Immunization of infected hamsters with SV40, irradiated SV40 hamster tumor cells, primary human embryo kidney cells, or hamster fetal cells always increased C-antibody levels over those in infected controls given no immunization. Adult primary human kidney cells, lyophilized SV40 tumor cells, or non-irradiated hamster fetal cells always diminished the C-antibody level below infected unimmunized controls. Lyophilized SV40 tumor cells, non-irradiated hamster fetal cells or adult human cells failed to induce immunity to SV40 tumor cell challenge and failed to interrupt SV40 oncogenesis. Fifty percent protection against SV40 tumor induction was seen among hamsters immunized with irradiated human embryo kidney cells, and 62% protection was afforded by immunization of adult hamsters with SV40. Irradiated SV40 tumor cells gave complete protection.

0718 REPLICATING SV40 MOLECULES CONTAINING CLOSED CIRCULAR TEMPLATE DNA STRANDS. (E.) Jaenisch, R. (Dept. Biochem., Princeton U., N.J.), A. Mayer and A. Levine. *Nature New Biology* 233(37):72-75, 1971.

Molecules of SV40 DNA in all stages of replication were isolated and shown to contain closed circular template strands with supercoil twists in addition to newly replicated DNA fragments. <sup>3</sup>H-labeled SV40 DNA was extracted from infected monkey cells and centrifuged to equilibrium in ethidium bromide CsCl gradients; early replicating molecules of SV40 DNA (10-70% of the replication completed) banded at densities between closed circular SV40 DNA and relaxed circular SV40 DNA. When these molecules were treated with pancreatic DNAase they banded at a lighter density. The SV40 DNA from the intermediate density region of the ethidium bromide CsCl gradient, after 7 min and 120 min <sup>3</sup>H-thymidine labeling periods, was recentrifuged in a second ethidium bromide CsCl gradient to remove contaminating closed circular viral and relaxed circular DNA. Purified intermediate density SV40 DNA was sedimented through an alkaline sucrose gradient. With 7 min pulses of <sup>3</sup>H-thymidine, fragments of labeled SV40 DNA shorter than unit length SV40 DNA were seen in alkaline sucrose gradients; with 120 min pulses, closed circular SV40 DNA was labeled as well as the newly repli-

cated shorter DNA fragments. Evidently, mature SV40 DNA molecules labeled during the 120 min pulse can initiate new rounds of replication so that template (closed circular) and progeny strands (DNA fragments) are labeled in a long pulse. Electron micrographs of early replicating DNA molecules showed replicating structures, with 2 branch points and 3 branches, having supercoil twists. Ambiguities or discontinuities at one or both replication forks were seen in the replicating molecules; these were thought to be single stranded regions. It was noted that if a single stranded region at a replicating fork was taken to indicate replication occurring at that site, then some at least of the SV40 DNA replicated bidirectionally.

0719 CELL LINE INITIATION FROM CORD BLOOD LEUKOCYTES TREATED WITH VIRUSES, CHEMICALS AND RADIATION. (E.) Chang, R. S. (Sch. Med., U. California, Davis), M.-W. Hsieh and W. Blankenship. *J Nat Cancer Inst* 47(2):479-483, 1971.

Blood was drawn from the umbilical cord of human subjects and attempts were made to establish umbilical cord blood leukocyte cultures by treating cord blood leukocytes in one of the following ways: addition to leukocytes of Kaplan cell filtrate (prepared from lymphoblastoid cells of an infectious mononucleosis patient), infection of leukocytes with SV40, exposure of leukocytes to 50 or 100 rads of X-irradiation, treatment of leukocytes with 3-methylcholanthrene, treatment with 4-nitroquinoline-1-oxide, treatment with 7,12-dimethylbenz(a)anthracene, treatment with dibenz(a,h)anthracene or treatment with nitrosodimethylamine. None of 45 cultures of umbilical cord leukocytes not given any treatment yielded an established cell line. Nineteen established cell lines evolved from 41 Kaplan cell filtrate-treated cord leukocyte cultures. Nine of these established lines degenerated before the first subculture; 3 lines grew actively in the 52nd, 60th and 61st subcultures. None of the X-irradiated cord leukocyte cultures, and none of the cultures treated with SV40 or with chemical carcinogens developed into established cell lines.

0720 CELL DIVISION IN MEDIUM LACKING SERUM GROWTH FACTOR: COMPARISON OF LINES TRANSFORMED BY DIFFERENT AGENTS. (E.) Smith, H. S. (Nat'l. Cancer Inst., Bethesda, Md.) and C. D. Scher. *Nature* 232(5312):558-559, 1971.

Various transformed lines of BALB/c 3T3 mouse cells which lacked density-dependent inhibition of growth were tested for their ability to grow in the absence of a DNA synthesis-initiating growth factor or factors. Transformed cells included cells transformed by SV40, Kirsten murine sarcoma virus, Moloney murine sarcoma virus and Rous sarcoma virus (strain Bratislava). Cells transformed

by X-irradiation (1500 rads) and by UV (2000 ergs mm<sup>-2</sup>) were also used. Virus-transformed cells grew well in media lacking the serum growth factor(s); all SV40-transformed lines had relative plating efficiencies of 20%-60%, as did clonal lines transformed by sarcoma virus. Only 3/8 of the non-virus-transformed cells grew well in factor-free media; 5 of the 8 non-virus-transformed lines had relative plating efficiencies of 2% or less.

0721 CONTACT-INHIBITED REVERTANT CELL LINES ISOLATED FROM SV40-TRANSFORMED CELLS: II. ULTRASTRUCTURAL STUDY. (E.) McNutt, N. S. (Harvard Med. Sch., Boston, Mass.), L. A. Culp and P. H. Black. *J Cell Biol* 50:691-708, 1971.

Contact-inhibited revertant mouse cells, normal 3T3 cells and SV40-transformed 3T3 cells were observed under the electron microscope; confluent and subconfluent cultures of normal and virus-transformed 3T3 cells were studied. Revertant cells were usually mononucleate but tended to form single- and multinucleated giant cells. Nuclear pleomorphism in revertant cells was striking. Nuclei of revertant cells showed more variation in morphology than did nuclei in normal 3T3 cells; normal cell nuclei were smaller than nuclei of revertant cells. Nuclei of transformed 3T3 cells were smaller than either revertant cell nuclei or normal cell nuclei. Deep infoldings of both membranes in the nuclear envelope of the nucleoplasm were more common in confluent virus-transformed 3T3 cells than in confluent normal 3T3 cultures or revertant cell cultures. The endoplasmic reticulum of normal 3T3 cells resembled that in revertant cells in confluent cultures. Endoplasmic reticulum in transformed cells was seldom organized into a branching system of cisternae and tubules; this arrangement was more frequently seen in revertant and in normal cells. Ectoplasm of both normal and revertant cells showed a prominent system of filaments 60-80 or 100 Å in diameter. Microtubules 250 Å in diameter were also common in the ectoplasm of normal and revertant cells. Virus-transformed cells had a relatively poorly developed system of ectoplasmic filaments. The abundance of these filaments correlated with contact inhibition of movement and growth of cells; fewer bundles of filaments were seen in growing cells than in contact-inhibited cells.

0722 ELECTRON MICROSCOPIC STUDY ON ACUTE THYMIC INVOLUTION INDUCED BY POLYOMA VIRUS INFECTION. (E.) Imamura, M. (Sapporo Med. Coll., Japan), T. Matsuyama, K. Toh and T. Okuyama. *J Nat Cancer Inst* 47(2):289-299, 1971.

Newborn strain AKR mice were infected with polyoma virus; when infected mice began to show symptoms of runting, they were killed and involuted thymuses were extracted and prepared for electron microscopy.



Involuted thymuses were marked by abundant nuclear debris derived from thymic lymphocytes (TL); TL were seen in cytoplasm of epithelial reticular cells and macrophages. TL nuclei showed a tendency to homogenization, and their nuclear chromatin was often condensed. Damaged TL nuclei often had irregular shapes resulting in nuclear segmentation. In TL cytoplasm in early stages of degeneration, polyribosomes disappeared and mitochondria were swollen. Osmiophilic dense structures were often seen in damaged TL cytoplasm and near the destroyed nuclei; these structures were of 2 types: structures of a serpentine configuration and structures appearing as a mass of entangled strands. Nuclei of epithelial reticular cells, and phagosomes of macrophages, often contained polyoma virus particles; epithelial cells with intranuclear virus particles contained many destroyed TL within the cytoplasm (although virus particles were not seen in cytoplasm). Virus particles in epithelial cell nuclei, together with the observed development of epithelial thymoma in adult virus-infected mice, suggested that epithelial cells in the thymus are susceptible to polyoma virus and are transformed just after polyoma virus infection in mice infected in the neonatal period. Polyoma virus particles were not seen around most of the destroyed TL, and direct viral participation in TL destruction was not evident.

- 0723 "UNBLOCKING" SERUM ACTIVITY *IN VITRO* IN THE POLYOMA SYSTEM MAY CORRELATE WITH ANTITUMOUR EFFECTS OF ANTISERUM *IN VIVO*. (E.) Bansal, S. C. (Pacific Northwest Ref. Fdn., Seattle, Wash.) and H. O. Sjogren. *Nature New Biology* 233(37):76-78, 1971.

The inhibition of the capacity of sera from tumor-bearing animals to prevent tumor cell destruction by immune lymphocytes *in vitro* was studied. The inhibition (or "unblocking") of this serum blocking activity was studied in sera from rats which had polyoma virus-induced tumors. A serum pool (A) was established from W/Fu rats which were given BCG injections s.c.; 2 wk after BCG, a polyoma tumor isograft was implanted. The subsequent tumor was removed and 7 days later rats were allografted with a polyoma tumor. To assay unblocking activity, serum A was mixed with a known blocking serum and the effect of the resulting mixture on the cytotoxicity of immune lymphocytes for polyoma tumor target cells was observed. Serum A, mixed with a blocking serum, caused a 68% decrease in the serum's blocking activity. Other sera (B-1 and C-1) came from 2 rats whose polyoma isografts had been surgically removed 5 days previously. Sera B-1 and C-1 abolished the blocking effect of a serum taken from the same rats before tumor excision and abolished the blocking effect of sera from other tumor-bearing rats as well. Three sera taken from rabbits inoculated with 2-4 doses of rat polyoma tumor cells had no blocking effect, but reduced the blocking activity of a rat blocking serum. Serum A was injected into 3-methylcholanthrene-induced sarcoma-bearing rats; in tumor-bearing rats

not given serum A, tumors grew progressively while in 4 of 5 rats given serum A tumors grew more slowly and eventually started to regress. No blocking activity was detected in sera of rats whose tumors had regressed, but serum from a rat whose tumor grew progressively developed blocking activity.

- 0724 INVERSE RELATIONSHIP OF POLYOMA TUMOUR SPECIFIC CELL SURFACE ANTIGEN TO H-2 HISTOCOMPATIBILITY ANTIGENS. (E.) Ting, C.-C. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and R. B. Herberman. *Nature New Biology* 232(30):118-120, 1971.

In tumors produced by polyoma virus, the quantity of H-2 antigens was found to vary inversely with the amount of tumor-specific cell surface antigen. Anti-polyoma antiserum (APS) was produced by immunization of C3H/3N mice with syngeneic polyoma tumor 4198. Two antisera (AHS<sub>1</sub> and AHS<sub>2</sub>) were produced in mice immunized against normal H-2 histocompatibility antigens. The isotopic antiglobulin technique was used to determine the antigenic content of various cell lines. In absorption experiments 0.4 ml of diluted antiserum was absorbed with different numbers of cells at 37°C for 1 hr. Normal serum at the same dilution was absorbed in the same manner. Cell lines employed included the 4094 cells derived from C3H/HeN parotid gland, 4198 cells produced by transformation of the 4094 cells with polyoma virus, and 4198 V cells derived from 4198 cells but carried for more generations in tissue culture and showing decreased oncogenicity in adult C3H mice. When APS and normal C3H serum at various dilutions were tested against 4198 and 4198V cells, consistently higher <sup>125</sup>I counts were obtained with 4198V cells. Absorption experiments showed that 4198V cells contained 8.8 times more of the tumor specific cell surface antigen than 4198 cells. In contrast, AHS was a multispecific antiserum for C3H cells and AHS<sub>2</sub> was probably monospecific for C3H cells. Direct testing with both of these sera gave higher <sup>125</sup>I counts with 4198V cells than with 4198 cells which suggested that 4198 cells had more normal H-2 antigens. Absorption experiments showed that 4198V cells had 4.5 times more of the H-2 antigens recognized by AHS, and 2.3 times more of the H-2 antigens recognized by AHS<sub>2</sub>. Both polyoma cell lines had much less H-2 than 4094 or C3H spleen cells.

- 0725 SEGREGATION OF MORPHOLOGICAL REVERTANTS IN POLYOMA-TRANSFORMED HYBRID CLONES OF HAMSTER FIBROBLASTS. (E.) Marin, G. (Imp. Cancer Res. Fund, London, England). *J Cell Sci* 9:61-69, 1971.

A series of hybrid clones was obtained by crossing untransformed B1 baby hamster kidney fibroblasts (BHK 21) with polyoma virus-transformed T6 clones, and by crossing untransformed T6 clones with transformed B1 clones. The B1 clone was resistant to

$10^{-4}$  M 5-bromodeoxyuridine and the T6 clone was resistant to  $3 \times 10^{-6}$  M 6-thioguanine (TG). The frequency of parental type segregants (i.e., cells resistant to TG or 5-bromodeoxyuridine) was measured in all hybrid clones and resistant colonies were scored for the presence of morphological revertants. Chromosomal segregants were produced by selecting for resistance to TG. Morphological revertants appeared among TG-resistant segregants in a minority of hybrid clones. In this system, morphological reversion arose independently of TG-resistance. Transformed and revertant colonies were isolated and grown up individually; each clone was tested for its ability to grow in agar medium and for the presence of polyoma virus-specific complement-fixing (CF) antigen. All revertant clones grew in agar with a very low efficiency. Polyoma virus-specific CF antigen was still present in some revertant clones; in other revertant clones, CF antigen was reduced to traces or was absent. The production of revertants appeared to be limited to an early phase in the life-history of the hybrid line. Morphological revertants showed a reduced chromosomal complement. Findings confirmed the hypothesis that morphological reversion occurred as a consequence of the loss of chromosomes concerned with the maintenance of the transformed phenotype.

- 0726 SYNTHESIS OF POLYOMA DNA BY ISOLATED NUCLEI. (E.) Winnacker, E. L. (Dept. Chem., Karolinska Inst., Stockholm, Sweden), G. Magnusson and P. Reichard. *Biochem Biophys Res Commun* 44(4):952-957, 1971.

Primary mouse kidney cells, 3T3 and 3T6 mouse cells were infected with polyoma virus; nuclei were isolated from infected cells and viral DNA synthesis in isolated nuclei was investigated. After virus infection, nuclei from contact-inhibited kidney and growing 3T3 cells incorporated 4 times more radioactivity from  $^3\text{H}$ -dTTP into DNA than did nuclei from mock-infected cells. DNA from infected cells was analyzed by centrifugation on neutral sucrose gradients; nuclei from contact-inhibited and growing cells produced a radioactive DNA which sedimented as a peak at 25S ahead of supercoiled polyoma virus DNA. This 25S peak was absent from DNA of mock-infected control cells which contained a slower-moving radioactive peak at about 10S. In hybridization experiments with radioactive DNA from infected kidney cells and polyoma virus and mouse DNA, the material from the 25S peak in infected cells behaved like true polyoma virus DNA while material from the 10S peak contained a mixture of mouse and polyoma DNA. It was concluded that the DNA sedimenting at 25S in infected cells was of viral origin. This DNA was similar to DNA which occurs in intact polyoma virus-infected cells and in SV40-infected cells, and which has been characterized as a replicative intermediate in the synthesis of viral DNA.

- 0727 VIRUS-LIKE PARTICLES IN L5178Y MURINE LEUKAEMIC CELLS. (E.) Narang, H. K. (Newcastle General Hosp., Newcastle upon Tyne, England), T. M. Bell and P. E. Gibson. *Europ J Cancer* 7:325-327, 1971.

- 0728 PRIMARY LYMPHOMA OF THE OVARY RESEMBLING BURKITT LYMPHOMA: (A CASE REPORT WITH REVIEW OF THE LITERATURE). (E.) Ramachandran, P. (Med. Coll., Trivandrum, India) and G. George. *Indian J Cancer* 7(2):143-146, 1970.

- 0729 LATENT HERPES SIMPLEX VIRUS IN SPINAL GANGLIA OF MICE. (E.) Stevens, J. G. (U. California Sch. Med., Los Angeles) and M. L. Cook. *Science* 173(3999):843-845, 1971.

- 0730 THE EFFECTS OF ORONASAL ADMINISTRATION OF TWO STRAINS OF MURINE SARCOMA VIRUS IN MICE. (E.) McCully, D. J. (Sch. Med., Perth, Western Australia), P. J. Simons and J. D. Ingram. *Int J Cancer* 8:107-112, 1971.

- 0731 CHARACTERIZATION OF FOUR NEW ADENOVIRUS SEROTYPES ISOLATED FROM CHIMPANZEE TISSUE EXPLANTS. (E.) Basnight, M. (Natl. Inst. Hlth., Bethesda, Md.), N. G. Rogers, C. J. Gibbs, Jr. and D. C. Gajdusek. *Amer J Epidemiol* 94(2):166-171, 1971.

- 0732 ALTERATION OF CELLULAR RNA SYNTHESIS AND PROCESSING IN TYPE 7 ADENOVIRUS-INFECTED KB CELLS. (E.) Shannon, W. M. (Tulane U. Sch. Med., New Orleans, La.) and S. Halperen. *J Gen Virol* 12:321-324, 1971.

- 0733 ELECTRONOPTIC DEMONSTRATION OF THE VIRUS IN EXPERIMENTAL MOUSE ERYTHROLEUKAEMIA. (E.) Mach, O. (Czechoslovak Acad. Sci., Prague) and J. Libansky. *Neoplasma* 18(4):349-353, 1971.



- 0734 FLUORESCENT CELL-COUNTING ASSAY OF ADENOVIRUS IN DIPLOID FIBROBLASTIC CELLS. (E.) Van Nieuwstadt, A. P. (Dept. Med. Microbiol., U. Nijmegen, Netherlands) and J. Van Der Veen. *Arch Ges Virusforsch* 34:136-143, 1971.
- 0735 THE FINE STRUCTURE OF CANINE GLIOMAS AND INTRACRANIAL SARCOMAS INDUCED BY THE SCHMIDT-RUPPIN STRAIN OF THE ROUS SARCOMA VIRUS. (E.) Vick, N. A. (Sec. Neurology, U. Chicago, Ill.), D. D. Bigner and J. P. Kvedar. *J Neuropath Exp Neurol* 30(3):354-367, 1971.
- 0736 BURKITT'S LYMPHOMA: (A REPORT OF 3 CASES FROM SOUTH INDIA). (E.) Date, A. (Christian Med. Coll. Hosp., Tamil Nadu, India), M. Mathan, A. S. Fenn and L. B. M. Joseph. *Indian J Cancer* 7(2):140-142, 1970.
- 0737 EFFECTS OF PHYSICAL FACTORS ON THE PRODUCTION OF AVIAN SARCOMA VIRUS B77 BY RAT TUMOUR CELLS 17RB177 AND CLONAL ANALYSIS OF THESE CELLS. (E.) Popovic, M. (Cancer Res. Inst., Bratislava, Czechoslovakia), M. Grofova and D. Simkovic. *Neoplasma* 18(3):257-263, 1971.
- 0738 INCOMPLETE SEDIMENTATION OF RAUSCHER LEUKAEMIA VIRUS PARTICLES DURING ULTRACENTRIFUGATION. (E.) Offers, S. (Radiobiol. Inst., Rijswijk, Netherlands) and P. Bentvelzen. *Europ J Cancer* 7(4):357-359, 1971.
- 0739 ASSOCIATION OF DEOXYRIBONUCLEASE-SENSITIVE MATERIAL WITH ADENOVIRUS PENTON AGGREGATES AFTER TREATMENT OF INFECTED CELL CULTURES WITH SODIUM DEOXYCHOLATE. (E.) Marusyk, R. G. (Karolinska Inst., Sch. Med., Stockholm, Sweden) and E. Norrby. *Canad J Microbiol* 17(8):1009-1013, 1971.
- 0740 STUDY OF THE *IN VIVO* FIXATION OF ANTIBODIES ON TUMORS PROVOKED IN HAMSTERS BY INJECTION OF SV40-TRANSFORMED CELLS (TSV<sub>5</sub>C1<sub>2</sub>). (E.) Sobczak, E. (Inst. Sci. Res. Cancer, Villejuif, France) and C. deV. St. Cyr. *Int J Cancer* 8:47-52, 1971.
- 0741 MORPHOLOGICAL STUDIES ON *Herpesvirus saimiri* IN SUBHUMAN AND HUMAN CELL CULTURES. (E.) Heine, U. (Natl. Cancer Inst., Bethesda, Md.), D. V. Ablashi and G. R. Armstrong. *Cancer Res* 31(7):1019-1029, 1971.
- 0742 ISOLATION OF A NON-FOCUS-FORMING AGENT FROM STRAIN MC29 AVIAN LEUKOSIS VIRUS. (E.) Langlois, A. J. (Duke U. Med. Ctr., Durham, N.C.), L. Veprek, D. Beard, R. B. Fritz and J. W. Beard. *Cancer Res* 31(7):1010-1018, 1971.
- 0743 THE INFLUENCE OF AGE ON CHRONIC REMITTENT FRIEND DISEASE. (E.) Dawson, P. J. (U. Oregon Med. Sch., Portland) and A. H. Fieldsteel. *Cancer Res* 31(7):974-980, 1971.

See also:

- \* (Rev): 0603, 0613, 0614, 0620, 0626  
 \* (Immun): 0752, 0756, 0764, 0767, 0768, 0769

- 0744 ENHANCED GROWTH OF PRIMARY MOLONEY VIRUS-INDUCED SARCOMAS IN MICE. (E.) Pierce, G. E. (Dept. Surg., U. Washington, Seattle). *Int J Cancer* 8:22-31, 1971.

Studies were designed to determine whether or not serum from mice with progressively growing Moloney virus-induced sarcomas had an enhancing effect *in vivo* on tumor growth. Serum was obtained either from BALB/c mice with progressively growing tumors or from mice with tumors persisting for more than 2 mo. after Moloney virus injection (these sera were designated "progressor" sera). Progressor sera were heat inactivated at 56°C and injected i.p. into mice 24 hr prior to injection of Moloney virus. Significant enhancement of tumor growth was obtained in mice given progressor serum; tumors in the progressor serum-pre-treated mice appeared about 2 days earlier than tumors in virus-inoculated controls given normal BALB/c serum. Tumors in the progressor serum-pre-treated group also achieved significantly greater size than tumors in controls. Even greater enhancement of tumor growth was obtained by the administration to mice of serum taken from Moloney virus-inoculated mice 4-5 days after their virus-induced tumors had begun to regress ("regressor" serum). In a related experiment regressor sera were taken from mice well after the completion of tumor regression and regressor mice were further immunized by a second injection of Moloney virus 11 days prior to bleeding. Regressor serum from these mice had no enhancing effect on tumor growth when injected into mice prior to virus inoculation; this regressor serum in fact significantly inhibited tumor growth. The specific serum factor(s) responsible for tumor growth enhancement by serum remain to be identified.

- 0745 TUMOR IMMUNITY IN INBRED MICE WITH PROGRESSIVELY GROWING SYNGENEIC TUMORS: A STUDY OF CONCOMITANT IMMUNITY. (E.) Deckers, P. J. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), B. W. Edgerton, B. S. Thomas and Y. H. Pilch. *Curr Top Surg Res* 3:371-384, 1971.

Experiments were designed to study the development of concomitant immunity and to determine its relationship to the size of the primary tumor and to the temporal interval between initial tumor transplantation and challenge of the tumor-bearing host with a test inoculum of cells from the same tumor. C57Bl/6 mice were inoculated in the right hind leg with  $10^5$  viable methylcholanthrene-induced sarcoma cells; 1 day after this initial tumor transplantation, some of the mice were given  $5 \times 10^3$  tumor cells in the left hind leg. At 7, 14, 21 and 28 days after the initial  $10^5$  tumor cell transplant, additional groups of tumor-bearing mice were challenged with  $5 \times 10^3$  tumor cells in the left hind leg. Challenge controls consisted of tumor-free mice which had not received an initial dose of  $10^5$  tumor cells, but which were given  $5 \times 10^3$  tumor cells on the same days as tumor-

bearing mice in the various challenge groups. Mice previously inoculated with  $10^5$  tumor cells rejected a second challenge inoculation of this tumor at all time intervals following initial tumor transplantation except for day 1. Challenge tumor inocula grew in 99-100% of recipients when implanted on day 1 after initial tumor transplantation. Tumors developed in 95-100% of mice in all challenge control groups. No decrease was seen in the growth rate of the initial tumor transplant in mice given a second challenge inoculum of tumor cells.

- 0746 FURTHER STUDIES ON THE EFFECT OF NEURAMINIDASE ON TUMOR CELL TRANSPLANTABILITY. (E.) Sanford, B. H. (Harvard Med. Sch., Boston, Mass.) and J. F. Codrington. *Tissue Antigens* 1:153-161, 1971.

Changes induced by neuraminidase in tumor transplantability were studied using a spontaneous mouse mammary adenocarcinoma (TA3); hosts for the study were syngeneic A/HeHa mice, and allogeneic C3H/St and DBA/2 Ha mice. Untreated TA3 cells killed 100% of syngeneic mice, 76% of allogeneic C3H mice and 100% of allogeneic DBA/2 mice. Treatment of cells with neuraminidase significantly reduced the number of deaths in allogeneic C3H hosts (39% of mice given treated TA3 cells died), but had little effect on transplantability in syngeneic hosts. No change in transplantability was seen if cells were treated with heat-inactivated neuraminidase. Thymectomized, irradiated, allogeneic C3H hosts showed no resistance to neuraminidase-treated TA3 cells. Transplantability of neuraminidase-treated TA3 cells did not appear to be related to decreased cell viability; there was no significant difference in trypan blue uptake between treated and untreated cells, and inocula of neuraminidase-treated cells produced tumors and killed syngeneic mice. Absorption studies with monospecific H-2 antisera directed against subcomponents 3, 4, 11 or 28 showed essentially the same absorption capacity for neuraminidase-treated or untreated TA3 cells, with both absorbing approximately as well as positive control strain A spleen cells. Over 50% of neuraminidase-treated TA3 cells were regularly killed by undiluted guinea pig serum in the absence of antibody, while untreated TA3 cells were not affected. C3H mouse serum was also highly destructive for neuraminidase-treated TA3 cells, although it had no effect on untreated TA3 cells. When guinea pig serum added as a source of complement in treating mouse sera was pre-absorbed with either agarose or neuraminidase-treated TA3 cells, toxic activity of sera was removed.

- 0747 IMMUNOLOGICAL SUPPRESSION OF THE OCCURRENCE OF SPONTANEOUS MAMMARY TUMORS IN



C3H/He MICE. (E.) Irie, K. (Tokyo Met. Okubo Hosp., Japan) and R. F. Irie. *Nature* 233(5315): 133-134, 1971.

Studies were performed to determine whether the occurrence of spontaneous mammary tumors in C3H/He mice was suppressed by immunization with the specific antigens of the mammary tumor. Tumor specific transplantation antigen of mouse mammary tumors, extracted from the ascitic line derived from a spontaneous mouse mammary tumor, was used to immunize 35 C3H/He mice. Another group of mice was given injections of extracts of visceral organs of strain C3Hf mice, and a third group was given no treatment. The occurrence of spontaneous mammary tumors in the first group was considerably suppressed compared with the second and third groups. About 30% of mice given tumor antigen had developed spontaneous mammary tumors by 32 months of age; mice given organ extracts and mice given no treatment developed tumors in 60% and 65%, resp., of cases by 32 months of age.

0748 BIOLOGIC PROPERTIES OF E MYELOMA PROTEINS. (E.) Ogawa, M. (Dartmouth Med. Sch., Hanover, N.H.), O. R. McIntyre, K. Ishizaka, T. Ishizaka, W. D. Terry and T. A. Waldmann. *Amer J Med* 51:193-199, 1971.

The isolation and purification of the E myeloma protein from the second E myeloma patient on record, and the physicochemical properties of this protein, were described. Serum taken from the E myeloma patient (patient P.S.) was dialyzed and applied to a column of DEAE-cellulose to purify the E myeloma protein (PS protein). The isolated protein gave a single gamma 1 precipitin band in immunoelectrophoresis against goat antihuman serum; no other protein could be detected. The physicochemical properties of the PS protein were identical with those of the E myeloma protein isolated from the serum of another patient with IgE myeloma (ND protein). PS protein and ND protein could not be distinguished on the basis of the antigenic structure of the Fc portion of the E myeloma protein. In double immunodiffusion studies, however, ND and PS proteins reacted differently to anti-ND protein antiserum, suggesting that ND protein had antigenic determinants which were not shared by PS protein; these antigenic determinants were thought to be located in the Fd portion of ND protein. Patient P.S. did not accept passive sensitization with reaginic antibodies in the Prausnitz-Kustner reaction; in the reversed Prausnitz-Kustner reaction, patient P.S. reacted only to the intradermal injections of high concentrations of anti-IgE. However, P.S. reacted normally to intradermal injections of histamine. The pattern for histamine release from leukocytes in patient P.S. was similar to that of nonatopic normal subjects. The metabolic patterns of PS and ND proteins were identical.

0749 HODGKIN'S DISEASE: EVIDENCE FOR A TUMOR ASSOCIATED ANTIGEN. (E.) Order, S. E. (Harvard Med. Sch., Boston, Mass.), M. Porter and S. Hellman. *New Eng J Med* 285(9):471-474, 1971.

Fresh nodules from the perisplenic nodes and splenic nodules of 2 patients with Hodgkin's disease (T. D. and J. G.) were prepared in cell suspensions; suspensions containing cells from tumor nodules were injected intradermally into rabbits. Three booster immunizations followed the initial immunization. A week after the last booster, intracardiac bleeding was performed on immunized rabbits. Antisera were absorbed with normal sera of the patient donating tumor nodule cells and incubated with freshly prepared spleen cells from the 2 Hodgkin's disease patients; adjacent normal spleen tissue from the patients was also absorbed with antisera. Indirect immunofluorescence was used to demonstrate a tumor-associated antigen in the Hodgkin's disease sections. When antisera were absorbed once or twice with normal spleen cells and incubated with tumor tissue, a demonstrable increased differential fluorescence was apparent, with the tumor-bearing regions in the tumor sections appearing bright yellow and the adjacent normal tissue showing no fluorescence. These results were obtained both when absorbed T. D. serum was tested against T. D. tumor and when absorbed J. G. serum was tested against J. G. tumors. Marked positive fluorescence was also seen in tumor-bearing regions when T. D. serum was absorbed with J. G. normal spleen cells and tested against J. G. tumor; a similar result was obtained when J. G. serum was absorbed with J. G. tissue and tested against T. D. tumor sections. Evidently a common antigenicity existed between the tumors of the 2 patients.

0750 ANTIBODY FORMATION BY BONE MARROW CELLS IN IRRADIATED MICE: I. THYMUS-DEPENDENT AND THYMUS-INDEPENDENT RESPONSES TO SHEEP ERYTHROCYTES. (E.) Playfair, J. H. L. (Middlesex Hosp. Med. Sch., London, England) and E. C. Purves. *Immunology* 21:113-121, 1971.

The IgM plaque-forming cell (PFC) response of transferred bone marrow cells was studied under various conditions in X-irradiated (NZB x BALB/c)F<sub>1</sub> mice; the effects on the PFC response of variations in the radiation dose and of variations in the concentrations of sheep red blood cell (SRBC) antigen were observed. Mice were given 400-1000 rads X-irradiation followed by injections of  $2 \times 10^7$  SRBC i.v. with or without added marrow and/or thymus cells prepared from syngeneic donors. In the absence of marrow or thymus cells there was an exponential fall in the PFC response with increasing radiation dose. When marrow cells were supplied higher PFC counts were found at all radiation doses. Above 800 rads the response by marrow cells alone, as well as the increase in the response produced by injecting thymus

cells together with marrow cells, was independent of radiation dose. In related experiments, mice exposed to 850 rads were given varying doses of SRBC injected together with marrow and thymus cells. The PFC response of marrow cells was greatest at high SRBC concentrations (e.g.,  $2 \times 10^6$  to  $2 \times 10^8$  SRBC), but the co-operative effect of thymus cells on the PFC response was most evident at lower SRBC levels. The co-operative effect of thymus cells was absent at high levels of SRBC (e.g.,  $2 \times 10^8$  SRBC). Increasing the number of marrow cells injected without increasing the number of thymus cells gave increasing numbers of PFC; however the dose-response curve did not suggest cell synergism. Since it was found that treatment of host or donor mice with thymectomy or with antithymocyte serum had no significant effect on the PFC response by marrow cells, it was concluded that the PFC response observed represented a genuine response by non-thymus-derived cells from the injected marrow.

- 0751 IMMUNOSUPPRESSION BY THE RADIATION LEUKEMIA VIRUS AND ITS RELATION TO LYMPHATIC LEUKEMIA DEVELOPMENT. (E.) Peled, A. (Weizmann Inst. Sci., Rehovot, Israel) and N. Haran-Ghera. *Int J Cancer* 8:97-106, 1971.

Normal C57BL/6 mice were immunized with sheep red blood cells (SRBC) and the production of 19S plaque-forming cells (PFC) by immunized mice was compared to the 19S PFC response in mice given thymic injections of radiation leukemia virus 30 days prior to SRBC immunization. A marked depression in 19S PFC response to SRBC was seen in virus-infected mice; on day 2 after SRBC, uninfected mice showed an average number of  $63 \pm 14$  PFC/ $10^8$  spleen cells while virus-infected mice showed  $15 \pm 10$  PFC/ $10^8$  spleen cells. In a related experiment, virus injected 1, 2 or 3 days before SRBC challenge, or simultaneously with SRBC, caused no decrease in the PFC capacity of mice; a marked decrease in PFC was seen when SRBC were given 5 days after virus injection. Serum hemagglutinin titers were depressed in virus-infected mice, but to a lesser degree than plaque forming capacity. No significant difference was observed in the survival time of skin grafts in virus-infected and uninfected mice and an engrafted fibrosarcoma failed to grow in either infected or uninfected mice. The graft-versus-host reaction test showed no defect in cellular immunity in virus-infected mice. The graft-versus-host reaction test showed no defect in cellular immunity in virus-infected mice. No correlation was found between the immunosuppressive effect of the radiation leukemia virus and lymphatic leukemia development. It was suggested that the decrease in the immune response to SRBC in normal C57BL mice, a decrease which grows more pronounced as the mice age, is due to radiation leukemia virus, which depresses the immune response in these mice, and which probably increases in titer as the mice grow older.

- 0752 CYTOTOXIC ANTIBODY REACTIVE WITH CULTURES OF LYMPHOID CELLS: OCCURRENCE IN DISEASE AND NORMAL HUMAN SERA. (E.) Herberman, R. B. (Natl. Cancer Inst., Bethesda, Md.) and J.-M. Nam. *J Natl Cancer Inst* 47(2):489-494, 1971.

Sera from African and American patients with leukemia, Burkitt's lymphoma, infectious mononucleosis and other malignant diseases were reacted with cells of the lymphoid tissue culture cell line Raji, which had been derived from a patient with Burkitt's tumor. Sera from about 1000 patients were assayed for cytotoxic antibody activity by observing the release of  $^{51}\text{Cr}$  from Raji target cells. Sera from normal Americans showed positive cytotoxic reactivity in 79% of cases. The percent of positive antibody reactions seen with sera from Burkitt's tumor patients was significantly higher than that seen with sera from matched African or American normal controls; sera from Burkitt's tumor patients reacted positively in 96% of cases. In contrast, the incidence of cytotoxic antibody in acute myelocytic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, multiple myeloma and infectious mononucleosis was significantly lower than the incidence of cytotoxic antibody in sera from normal Americans. The incidence of cytotoxic antibody in sera of leukemia patients was analyzed for a possible relationship to the number of peripheral leukocytes; the antibody level in sera from chronic leukemia patients was inversely related to the peripheral leukocyte count. In patients with infectious mononucleosis the incidence of cytotoxic antibody-positive serum reactions was lower during the acute phase of the illness than during convalescence. The incidence of cytotoxic antibody was lower in healthy American and African children under 5-yr-old than in older healthy controls. The cytotoxic antibody was thought to be an IgG immunoglobulin.

- 0753 KARYOTYPIC AND SURFACE FEATURES OF MURINE TA3 CARCINOMA CELLS DURING IMMUNOSELECTION IN MICE AND RATS. (E.) Hauschka, T. S. (Roswell Park Mem. Inst., Buffalo, N.Y.), L. Weiss, B. A. Holdridge, T. L. Cudney, M. Zumpft and J. A. Planinsek. *J Natl Cancer Inst* 47(2):343-357, 1971.

Growth characteristics of 3 sublines of a virulent hyperdiploid TA3 mouse and rat ascites tumor were observed; the TA3 mouse strain, derived originally from a mammary adenocarcinoma in an A/HeHa mouse, was lethal for and interchangeable among syngeneic and allogeneic mice and 4 strains of rats. The TA3 tumor showed remarkable cytogenetic stability, both in mice and rats, and in tissue culture; 950 chromosome counts in the near-diploid range were found and there was no numerical or structural departure from the chromosome pattern recorded for the original TA3 tumor from which sublines were derived. The TA3 tumor had a hyperdiploid mode of 41 acrocentrics and resembled the standard chromosome set for the female mouse except for 1 addi-



tional small autosome. The rat-adapted TA3 carcinoma resembled the mouse-adapted TA3 karyotypically; however the rat tumor had a large submetacentric marker chromosome. During prolonged heterologous immunoselection it lost several H-2<sup>a</sup> antigens expressed on TA3 cells from syngeneic A/Ha mice; these antigens remained undetectable by hemagglutinin absorption and after incubation with neuraminidase. Since peripheral sialomucin could conceivably interfere with the full penetrance of antigenic phenotype, TA3 cells were preincubated with neuraminidase. Although enzyme treatment consistently reduced the electrophoretic mobilities of TA3 cells by about 60%, it neither inactivated nor unmasked H-2<sup>a</sup> and H antigens on the tumor cell surface. The net negative surface charge on TA3 cells was apparently not correlated with degree of malignancy and antigen disparity.

0754 THE RELATIONSHIP BETWEEN IMMUNITY AND TOLERANCE: II. (E.) Graff, R. J. (Washington U. Sch. Med., St. Louis, Mo.). *Curr Top Surg Res* 3:363-370, 1971.

The time-dose relationship of the cellular immune response to the H-7 antigen was investigated in C57BL/10Sn mice and in B10.C(47N) mice. These strains are congenic resistant strains which define the H-7 locus; B10.C(47N) mice possess the H-7<sup>b</sup> allele, and were used as donors of lymphoid cells and skin grafts, while C57BL/10Sn mice possess the H-7<sup>a</sup> allele and were used as hosts. Thymic and splenic cell suspensions from B10.C(47N) mice were injected into C57BL/10Sn mice in amounts of  $5 \times 10^3$  -  $5 \times 10^8$  cells/mouse. The immune response to each quantity of antigen was assayed by skin grafting 1-98 days postinjection. The  $5 \times 10^6$  cells/mouse dose was consistently an immunizing dose (i.e., this dose resulted in accelerated rejection of grafts) and the  $5 \times 10^8$  cells/mouse dose was essentially a tolerance-producing dose (i.e., this dose resulted in persistence of skin grafts). The threshold-immunizing dose of lymphoid cells was found to be  $5 \times 10^5$  cells/mouse. The borderline tolerance-producing dose of lymphoid cells was  $5 \times 10^7$  cells/mouse. The immune response against the H-7 antigen appeared to reach a maximum about 28 days after antigen challenge and persisted for the duration of the study.

0755 SKIN-GRAFT REJECTION DURING LYMPHOMAGENESIS IN URETHAN-TREATED MICE. (E.) Parmiani, G. (Inst. Cancer Res., Philadelphia, Pa.). *J Nat Cancer Inst* 47(3):569-573, 1971.

The relationship between homograft response and lymphoma development in mice exposed to urethan was investigated; the immune status of urethan-treated mice was observed during the first part of

the lymphoma latent period. Female C57BL/6 mice were given 5 i.p. injections of 1 mg/kg body wt urethan at 2-day intervals. Treated mice were given grafts of skin from male C57BL/6 mice 17 and 42 days after the last administration of urethan since the first lymphomas were known to appear within 90-100 days from the last urethan treatment. Urethan proved strongly immunodepressive in both groups of mice. Among mice given skin grafts 17 days after urethan, the survival of skin grafts was prolonged for as long as 40 days by comparison to skin graft survival in controls not given urethan. Among mice given skin grafts 42 days after urethan the difference in skin graft survival time between treated and untreated mice dropped to 23 days. These results were thought to reflect a partial but significant recovery of cell-mediated immunity in the mice given skin grafts 42 days after urethan. No correlation between capacity to reject the graft and lymphoma development was found in either group of urethan-treated mice.

0756 ESTABLISHMENT OF CELL LINES FROM NORMAL ADULT HUMAN BLOOD LEUKOCYTES BY EXPOSURE TO EPSTEIN-BARR VIRUS AND NEUTRALIZATION BY HUMAN SERA WITH EPSTEIN-BARR VIRUS ANTIBODY. (E.) Miller, G. (Yale U. Sch. Med., New Haven, Conn.), H. Lisco, H. I. Kohn and D. Stitt. *Proc Soc Exp Biol Med* 137(4):1459-1465, 1971.

Experiments were designed to determine whether the capacity of strains of human lymphoblastoid cell lines (HLCL) to transform leukocytes correlated with the presence of detectable Epstein-Barr virus (EBV) antigen in the HLCL. Cells of an HLCL were given 4500 rads of X-irradiation and cocultivated with peripheral blood leukocytes (WBC) from normal donors. Alternatively, HLCL were inactivated by freezing and thawing and mixed with WBC. The induction of continuous proliferation of WBC by inactivated HLCL was observed. Cell line formation did not occur in 72 control cultures of WBC alone, or in 114 cultures inoculated with HLCL inactivated by X-irradiation or by freezing and thawing. Cell line formation was evident only in cultures containing both an inactivated HLCL (or extract) and WBC. The frequency of transformation varied and depended on the source of the transforming factor. Of 11 HLCL tested, only 6 were capable of inducing continuous proliferation of WBC; 3 HLCL with the capacity to transform WBC were derived from leukemic children. A correlation was found between the presence of EBV antigen and the capacity of an HLCL to transform. The 6 HLCL which provided the transformation factor all contained EBV antigen. Three HLCL without EBV antigen, and 1 with a barely detectable EBV antigen level, did not transform WBC. Only 1 line with a significant amount of EBV antigen was incapable of transforming WBC (this line was derived from a Burkitt's lymphoma). EBV antigen was found in 20 of 26 individual cultures of transformed normal leukocytes. Evidence suggested that mycoplasma in HLCL lines were not essential for trans-

formation of WBC. In a related experiment, it was found that 6 human sera containing anti-EBV antibody inhibited transformation and 5 sera free of antibody permitted transformation to occur.

- 0757 CONCOMITANT TUMOR IMMUNITY AND IMMUNO-SELECTION OF METASTASES. (E.) Sugarbaker, E. V. (Nat'l. Cancer Inst. Inst. Hlth., Bethesda, Md.), A. M. Cohen and A. S. Ketcham. *Curr Top Surg Res* 3:349-361, 1971.

Antigenic differences between an immunogenic primary rat sarcoma and its metastases were investigated. Rats were injected i.m. in a leg with cells of a spontaneously metastasizing immunogenic benzo(a)-pyrene-induced fibrosarcoma; 20 days later, when tumors and pulmonary metastases had formed, primary tumors were amputated to prolong survival and to allow for growth of large metastases. Primary tumors from 4 rats, and 3 pulmonary metastases from 1 rat, were minced and cell suspensions were prepared. Primary tumor and metastatic tumor cell suspensions were inoculated into thighs of 4 groups of 50 rats. Tumors from rats inoculated with primary tumor cells or with metastatic tumor cells were amputated and the immunized rats were challenged with cell suspensions of primary tumor or metastases. Suspensions of metastatic tumors "took" in 27 of 30 unimmunized controls and in none of 10 rats immunized with metastatic tumor cell suspensions. Primary tumor cell transplants took in 21 of 30 controls and in none of 10 primary tumor-immunized rats. However, there was no significant inhibition of tumor incidence in animals immunized with the primary tumor and challenged with metastatic tumor cells. Evidently, cell suspensions derived from transplanted metastases grew uninhibited in rats immunized with the primary tumors. All cell lines were immunogenic and some antigenic cross-reactivity between metastases was demonstrated. Using the mixed spleen-cell, tumor-cell neutralization assay, concomitant immunity was demonstrated at about the time metastases were forming. It was thought that concomitant immunity may provide for the immunoselection of antigenically altered metastatic cells in this system.

- 0758 CHANGES IN LYMPHORETICULAR TISSUES DURING GROWTH OF A MURINE ADENOCARCINOMA: III. PLAQUE-FORMING CELL RESPONSE IN LYMPH NODES AND SPLEEN. (E.) Rowland, G. F. (St. Bartholomew's Hosp., London, England), A. J. Edwards, C. M. Hurd and M. R. Sumner. *J Nat Cancer Inst* 47(2):321-327, 1971.

A mammary adenocarcinoma was transplanted into DBA/2J mice by s.c. implantation and the plaque-forming cell (PFC) response of tumor-bearing mice to injections of sheep red blood cells (SRBC) was monitored in

spleen and lymph nodes. The lifespan of tumor-bearing mice was 29.4 days. Control mice were not given tumor implants but were injected with SRBC. Changes in the PFC lymph node response were monitored from 4 days after SRBC immunization. Initially, the PFC response in lymph nodes rose at days 7 and 10 of tumor growth; after 15 days of tumor growth, the PFC response fell by up to 38% in the terminal stages of malignancy. Changes in the response to SRBC during the tumor growth period were measured in the spleen 4 days after immunization. The number of PFC's/ $10^6$  spleen cells rose slightly compared to controls by day 11 of tumor growth but then fell sharply, reducing the immune response by over 90% during the last wk of malignancy. The total number of PFC/spleen increased to nearly double the control levels by 17 days of tumor growth and then decreased sharply to 70% below controls during the last wk of malignancy. To determine if changes in the spleen response were due to variations in numbers of immunocompetent spleen cells,  $10^6$  spleen cells were transferred to heavily irradiated (e.g., 800 rads) recipient mice together with SRBC and the PFC response was determined after 7 days. A large and significant increase in PFC was seen. Thus, despite the fall in immune response to SRBC in tumor-bearing mice, the numbers of potentially immunocompetent cells/spleen were increased in tumor-bearing mice.

- 0759 SERUM  $\alpha$ -FETOPROTEIN IN HEPATOMA PATIENTS AFTER LIVER TRANSPLANTATION. (E.) Alpert, E. (Harvard Med. Sch., Boston, Mass.), T. E. Starzl, P. H. Schur and K. J. Isselbacher. *Gastroenterology* 61(2):144-148, 1971.

Serum  $\alpha$ -fetoprotein (AFP) levels were determined in 5 patients with liver carcinoma who underwent hepatectomy and liver transplantation. In 3 patients the slow growth of residual tumors after transplantation was correlated with low posttransplantation AFP levels (1-5 mg/100 ml serum). In 1 patient a sharp increase in AFP level following transplantation preceded clinical evidence of rapid tumor growth. In another patient the clinical course following transplantation indicated a possible cure; AFP levels in this patient declined to zero by 6 mo. posttransplantation. Immunosuppressive therapy, transplant rejection episodes and infection did not alter the levels of serum AFP in any of the patients. These studies suggest that serial AFP levels are a helpful prognostic guide in assessing residual tumor or tumor recurrence after liver transplantation.

- 0760 CHANGES IN LYMPHORETICULAR TISSUES DURING GROWTH OF A MURINE ADENOCARCINOMA: II. NUCLEIC ACID CONTENT AND SYNTHESIS IN LYMPH NODES, SPLEEN, AND THYMUS. (E.) Edwards, A. J. (St. Bar-



tholomew's Hosp., London, England), G. F. Rowland, M. R. Sumner and C. M. Hurd. *J Nat Cancer Inst* 47(2): 313-320, 1971.

Mice of the DBA/2J strain were implanted with a mammary adenocarcinoma and the wt, protein content, nucleic acid content, and nucleic acid synthesis in lymph nodes, spleen and thymus were observed. In tumor-bearing mice, lymph node wet wt and protein content increased by 140% of these values in non-tumor-bearing mice (controls) by 10 days of tumor growth. Lymph node DNA content increased by the same amount over 15 days of tumor growth, then fell to below control levels by day 23. DNA-synthesizing capacity of lymph nodes showed an increase of 50% over control values during the first 13 days of tumor growth; between days 13-20, the capacity of lymph node tissue to incorporate precursors into DNA increased to 250% of control levels. Lymph node RNA content rose in 7 days of tumor growth to 170% of control values, remaining at 150% of control at 23 days. RNA-synthesizing capacity changed little over the first 13 days. The RNA/DNA ratio in lymph nodes was increased in tumor-bearing mice, and an influx of RNA-rich cells was suggested. Spleen DNA content increased in the first 10 days of tumor growth; there was no change in spleen DNA synthesis. In a second phase (10-15 days) DNA synthesis increased rapidly and remained elevated. By 31 days, spleen DNA content showed signs of falling to control levels. Spleen RNA content rose to 6.5 times control level by day 24, then fell to less than 4 times control level by 31 days. RNA-synthesizing capacity of spleen showed no increase over the first 13 days, increased to more than double control values between 14-23 days, then returned to control levels by 27 days. After an initial fall in DNA content during the first 5 days of tumor growth, thymic tissue recovered from 7-14 days, falling thereafter to 60% less than control values. DNA-synthesizing capacity in thymus was virtually unchanged until 13 days, after which it fell off, showing an 80% decrease by 24 days. Thymic RNA content fell after 13 days, reaching a low of 50% of control values by 20 days. Thymic RNA-synthesizing capacity showed a slight rise at 10 and 13 days, then fell rapidly; after 31 days, it had fallen by over 90%.

determine which tissue specimens contained CEA. Fifteen of 18 primary and metastatic GI tract adenocarcinomas gave positive results for CEA; none of 38 tissue specimens from patients with benign disease or from patients with malignancies of sites other than the GI tract gave positive anti-CEA reactions. None of the samples of normal tissue taken from patients with GI tract adenocarcinoma reacted positively.

0762 TRANSITORY CELL ANTIGENS OF RAT LIVER. I. SECRETION AND SYNTHESIS OF FETAL SERUM PROTEINS DURING HEPATIC DEVELOPMENT AND REGENERATION. (Fr.) de Nechaud, B. (Inst. Cancer Res., Villejuif, France), J. Uriel. *Int J Cancer* 8:71-80, 1971.

The dynamics of  $\alpha$ -fetoprotein ( $\alpha$ -FP) in sera of pregnant, embryo and newborn rats under physiological and compensatory regeneration conditions of the liver were investigated. Quantitative immunoprecipitation with rabbit antisera showed that serum  $\alpha$ -FP levels in pregnant rats depended on the stage of pregnancy and on the number of fetuses in gestation. An increase in serum  $\alpha$ -FP occurred between the 13<sup>th</sup> and 17<sup>th</sup> day of pregnancy followed by a sudden decrease on the 19<sup>th</sup> day of pregnancy; an increase subsequently occurred which maintained a higher level of serum  $\alpha$ -FP through the day of delivery.  $\alpha$ -FP disappeared from female rat sera within 6 days following delivery. Fetal serum showed an increasing trend in  $\alpha$ -FP through the 18<sup>th</sup> day of gestation, a one day decrease and a peak value before birth. The  $\alpha$ -FP concentrations decreased slowly after birth and disappeared after 30 days of extrauterine life. Compensatory regeneration of the liver in both adult and 30-50-day old rats was produced following acute i.p. treatment with carbon tetrachloride (0.025 ml/200 g body wt), cadmium sulfate (0.1 mg/100 g body wt) or D-galactosamine chlorhydrate (25 mg/100 g body wt). Disappearance of  $\alpha$ -FP from young rat sera could be delayed by 15 days following CCl<sub>4</sub> administration. Reappearance of  $\alpha$ -FP in rats between 30 and 50 days of age could be seen following a series of CCl<sub>4</sub> injections. On the contrary, no  $\alpha$ -FP occurred under similar conditions of treatment in adult rats. The reoccurrence of  $\alpha$ -FP in rats below 40 days-of-age is attributed to activation processes of cell clones that had not been yet completely differentiated. Such clones seem to persist in 25% of rats through the age of 40 days.

0761 A STUDY OF TUMOR-SPECIFIC ANTIGENS OF THE HUMAN DIGESTIVE SYSTEM. (E.) Meeker, W. R., Jr. (U. Kentucky Coll. Med., Lexington) and J. A. Freer. *Curr Top Surg Res* 3:391-399, 1971

Specimens of normal and malignant human digestive system tissue were examined for the presence of the "carcinoembryonic antigen" (CEA). Tumor tissue from GI tract adenocarcinoma patients and from patients with conditions other than adenocarcinoma, and normal human tissue samples, were incubated with anti-CEA antiserum which had been prepared by injecting rabbits with tumor tissue extracts known to contain CEA. Ring or interfacial tests for detection of precipitating antibody were employed to

0763 ABO BLOOD GROUP DISTRIBUTION IN CARCINOMA BREAST. (E.) Rai, S. (Govt. Med. Coll., Patiala, India), K. C. Saronwala, P. K. Mittal and S. Arora. *Indian J Cancer* 7(2):135-139, 1970.

ABO blood group typing was performed on 100 patients with mammary carcinoma and the distribution of the blood groups in the carcinoma patients was compared with the blood group distributions in a series of 4275 healthy subjects. A statistically significant preponderance of the A blood type was found in the cancer patients; 33% of cancer patients were of type A while 21.9% of healthy controls were of type A. Blood groups O and AB were less common in cancer patients than group A; however, the differences between patients and controls with respect to these 2 blood types were not statistically significant. Of type A cancer patients, 42.9% were in the 40-50-yr-old age group. Breast cancer in type A patients appeared to have had a rapid onset; the duration of the disease was less than 6 mo. in 75.8% of type A patients.

0764 A LONGITUDINAL COMPARISON OF ANTIBODIES TO EPSTEIN-BARR VIRUS AND CLINICAL PARAMETERS IN CHRONIC LYMPHOCYTIC LEUKEMIA AND CHRONIC MYELOCYTIC LEUKEMIA. (E.) Levine, P. H. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.), D. A. Merrill, N. C. Bethlenfalvay, L. Dabich, D. A. Stevens and D. E. Waggoner. *Blood* 38(4):479-484, 1971.

A study was designed to determine whether the progression of disease in patients with chronic lymphocytic leukemia (CLL) was associated with changes in the levels of antibody to Epstein-Barr virus (EBV); a group of patients with chronic myelocytic leukemia (CML) was also studied to compare results obtained in a chronic lymphoproliferative disorder with those obtained in a chronic myeloproliferative disorder. Sera from 34 patients with CLL and from 20 CML patients were tested for EBV antibody by indirect immunofluorescence; sera from clinically normal subjects matched for age and sex with the CLL patients were taken as controls. A comparison of EBV titers in the leukemic patients and in normal individuals showed that the geometric mean titer of CLL patients (1:444) was significantly higher than that of CML patients (1:84) and significantly higher than that of normal controls (1:87). No significant anti-EBV antibody changes were detected in the 20 CML patients or in 23 of the 24 CLL patients followed for up to 5 yr. Apparently, the elevated EBV titer seen in patients with CLL reflected an event or process occurring before the onset of disease or occurring in the very early stages of disease and did not reflect a nonspecific rise paralleling an increase in total body lymphocytes.

0765 CYTOTOXIC FACTORS IN INHIBITION OF LYMPHOCYTE TRANSFORMATION IN LYMPHOMATA. (E.) Langner, A. (Warsaw Med. Acad., Poland), M. Pawinska-Proniewska, W. Glinski and S. Maj. *Brit J Derm* 85 (1):7-13, 1971.

The mechanism of inhibition of blastic transformation of phytohemagglutinin-stimulated lymphocytes in malignant lymphoreticular proliferation was investigated. Lymphocytes from patients with lymphoreticular malignancies and from normal subjects were incubated with either patients' plasma or plasma from normal subjects and the blastic transformation of phytohemagglutinin-stimulated lymphocytes in each of the 4 incubation conditions was monitored. Patient donors of lymphocytes and plasma included patients with lymphosarcoma, reticulosarcoma, chronic lymphatic leukemia, Hodgkin's disease and mycosis fungoides. Plasma from reticulosarcoma patients depressed the transformation of lymphocytes from reticulosarcoma patients and also depressed the transformation of normal lymphocytes; lymphocytes from reticulosarcoma patients showed increased transformation when incubated with normal plasma. Plasma from lymphosarcoma patients depressed transformation of lymphosarcomatous lymphocytes; lymphosarcoma patients' plasma also inhibited transformation of normal lymphocytes. Normal plasma enhanced transformation of lymphosarcoma patients' lymphocytes. Normal plasma did not enhance transformation of lymphocytes from chronic lymphatic leukemia patients; plasma from leukemia patients did inhibit the transformation of normal lymphocytes. Normal plasma increased the number of transforming Hodgkin's disease patients' lymphocytes; Hodgkin's disease plasma inhibited transformation of patients' lymphocytes, and inhibited transformation of normal lymphocytes in some cases but not in others. Plasma from patients with mycosis fungoides did not affect lymphocyte transformation, and transformation of mycosis fungoides patients' lymphocytes was not improved by incubating them with normal plasma. Apparently, inhibition of transformation of lymphocytes from patients with lymphosarcoma, reticulosarcoma and Hodgkin's disease depended on factors present in patients' plasma; on the other hand, inhibition of transformation of lymphocytes from chronic lymphatic leukemia patients was related to the lymphocytes and is not unblocked by using plasma of healthy individuals.

0766 B.C.G. VACCINATION AND LEUKAEMIA: EVIDENCE OF VITAL STATISTICS. (E.) Kinlen, L. J. (Radcliffe Infirm., Oxford, England) and M. C. Pike. *Lancet* 2(7721):398-402, 1971.

Leukemia mortality among infants and persons under 20-yr-old in Quebec and in Glasgow was compared to leukemia mortality in Canada excluding Quebec and in Scotland excluding Glasgow. Quebec has a policy of vaccinating children with *Bacillus Calmette-Guerin* (BCG), a policy which is not shared by the rest of Canada. Similarly, BCG vaccination of children is practiced in Glasgow but not in the rest of Scotland. In spite of a report from Quebec that BCG vaccination halved the risk of leukemia in children, no consistent or appreciable difference was found in the number of children dying from leukemia in any age group up to 20-yr-old between 1950-1969 in Quebec and the rest of Canada. Again, leukemia



mortality at ages 0-4-yr-old was similar in Glasgow and in the rest of Scotland. In Glasgow, leukemia mortality was lower for ages 5-9- and 10-14-yr-old; however the decline was most striking before children could have been vaccinated with B.C.G., and the mortality ratio rose at the same time as vaccination increased.

0767 IMMUNOLOGICAL STUDIES ON A HAMSTER-SPECIFIC SARCOMA VIRUS. (E.) Bomford, R. (Imp. Cancer Res. Fund Labs., London, England). *Int J Cancer* 8:53-60, 1971.

The antigenic relationship between Harvey murine sarcoma virus (H-MSV) and a hamster-specific sarcoma virus designated H-MSV (HaLV) was studied by comparing the internal group-specific (gs) antigens of the 2 viruses by immunodiffusion. H-MSV (HaLV) had been released from cells of H-MSV-induced hamster tumors. H-MSV (HaLV) and H-MSV appeared to possess different internal antigens. However, anti-H-MSV (HaLV) serum detected a hamster leukemia virus (HaLV) gs antigen, indicating that H-MSV (HaLV) had the HaLV gs antigen. It was concluded that H-MSV (HaLV) was an HaLV pseudotype of H-MSV. HaLV gs antigen was not detectable in non-producer BHK/21 hamster cells transformed by H-MSV (HaLV), or in Rous sarcoma virus-, polyoma- or SV40-transformed cells. Four transplanted hamster tumors, including a fibrosarcoma, a melanoma, a renal adenocarcinoma and a lymphoma, were found to contain HaLV gs antigen.

0768 IMMUNOLOGICAL STUDIES ON THE RADIATION LEUKAEMIA VIRUS IN C57BL MICE. (E.) Peled, A. (Weizmann Inst. Sci., Rehovot, Israel) and N. Haran-Ghera. *Nature* 232(34):244-245, 1971.

The production of neutralizing antibodies against the radiation leukemia virus was investigated in C57BL/6 mice; the feasibility of adoptive transfer of immunity against leukemic cells induced by radiation leukemia virus was demonstrated. Male mice were given thymic injections of radiation leukemia virus; 2 wk later, injected mice were bled and anti-virus antisera were collected. Radiation leukemia virus was mixed with anti-virus antiserum or with phosphate buffered saline (PBS) and injected into the thymuses of mice; 2 days after injection of the virus:serum mixtures, mice were exposed to 400 r of X-irradiation. Leukemia developed in 85-95% of mice given mixtures of virus and PBS while only 5-10% of mice given virus:antiserum mixtures developed leukemia. In a related experiment, virus:antiserum or virus:PBS mixtures were injected into thymuses of mice 30 days prior to s.c. challenge with viable leukemic cells from isologous lymphomas induced by radiation leukemia virus. Tumor cell transplants 'took' in

17% of challenged mice given virus:PBS mixtures and in 95% of mice given virus:antiserum. This finding suggested that the anti-radiation leukemia virus antiserum neutralized the virus and that the neutralizing serum contained antiviral antibodies. In a third experiment, mice were given thymic injections of virus or PBS and lymphoid cells from these mice were collected, mixed with leukemic cells, and injected s.c. into isologous mice; other recipient mice were given mixtures of immune and leukemic cells. Lymphoid cells taken from normal mice did not affect the growth of leukemic cells in these mice. However, lymphoid cells from donors preimmunized against radiation leukemia virus and immune serum from pre-immunized mice, decreased or prevented tumor cell takes. Apparently a common antigen or antigens were shared by radiation leukemia virus and by leukemic cells transformed by this virus.

0769 ALTERATION OF SKIN IN GROSS LEUKEMIA: II. KINETIC, PRELEUKEMIC, AND IRRADIATION STUDIES. (E.) Mariani, T. (Radiat. Therapy Res. Labs., U. Minnesota, Minneapolis), Y. Maruyama and R. A. Good. *J Nat Cancer Inst* 47(2):361-366, 1971.

Studies indicated that tumor cells were intimately involved in both rejection and tumor development at the graft site in C3H/Bi, DBA/2, and (C3H/Bi x DBA/2) F<sub>1</sub> mice given skin grafts of Gross lymphoma under various conditions. Skin from animals bearing a lymphoma in the ascites form for 12 hr or up to 10 days was transferred to normal syngeneic recipients. The frequency of skin graft rejection by recipients of skin from donors bearing a tumor for 4 days increased significantly over that for animals receiving transplants from donors bearing a tumor for 2 days -- 80 versus 25%, resp. Comparable findings were obtained for tumor development at the graft site; the frequency of tumor development in recipients of skin from donors bearing a tumor for 4 days increased over that in animals receiving transplants from donors bearing a tumor for only 2 days -- 90 versus 40%, resp. Experiments manipulating the presence of tumor cells in skin grafts were also conducted. Skin from Gross passage A virus-induced preleukemic mice (which was assumed to harbor no tumor cells) was grafted onto normal recipients. In a series of 49 transplants, 4 normal syngeneic mice rejected the skin graft and 45 accepted it; all 49 eventually died of leukemia. Evidently, skin had not undergone virus-induced antigenic change. In previous experiments, it had been found that a high percentage of animals rejected skin which was full of tumor cells, a finding which confirmed that tumor cells were involved in the graft rejection. Further experiments, in which mice were engrafted with skin from X-irradiated tumor-bearing mice, or in which skin from mice given irradiated ascites tumor was transplanted, substantiated the conclusion that the tumor cell itself was a major factor in the rejection phenomenon.

- 0770 SIMPLE RADIAL IMMUNODIFFUSION STUDIES OF SERUM PROTEINS IN LEUKEMIC PATIENTS. (It.) Spina, A. (Catania U., Italy), G. Silvia, G. Siragusa and B. Buonocore. *Haematol Arch* 55(2):153-162, 1970.

Simple radial immunodiffusion was applied for the determination of the IgA, IgM, IgG, haptoglobin and  $\alpha_2$ -macroglobulin fractions in the serum of 15 patients (3 with chronic lymphatic leukemia, 6 with chronic myeloid leukemia, 3 with myeloblastic leukemia, 2 with hemocytoblastic leukemia and 1 with monocytic leukemia). According to previous experience, the following values were referred to as normal: 50-120 mg% for IgM, 150-250 mg% for IgA, 1,000-1,500 mg% for IgG, 180-250 mg% for  $\alpha_2$ -macroglobulin and 220-300 mg% for haptoglobin. The data obtained by immunodiffusion were then compared with the electrophoretic pattern of the respective sera. A consistent increase in immunoglobulins was found in sera from patients found to be in an acute stage of the disease (7 of 8 cases); thus IgA ranged from 260 to 560 mg%, IgM ranged from 67 to 450 mg% and IgG ranged from 1,760 to 3,600 mg%. Haptoglobin was increased from 326 to 717 mg% in all patients found to go through an acute stage and in 2 patients with chronic myeloid leukemia. Alpha<sub>2</sub> macroglobulin increased (430-588 mg%) in sera from patients with monocytic, myeloblastic and in 1 case of myeloid leukemia which passed through an acute stage. The electrophoretic proteinogram showed increased  $\alpha$ -globulin values in all 6 cases going through an acute stage of leukemia. Gamma-globulins appeared to be within the norm electrophoretically in 4 of these 6 cases while all immunoglobulins were shown to be increased by the immunodiffusion test. Of the 4 patients with chronic myeloid leukemia 1 had a normal serum electrophoretic pattern but he revealed increased IgG values according to the immunodiffusion test. Dysproteinemia with increased  $\alpha$ -globulin values appeared in the electrophoretic pattern of the other 3 patients; this increase corresponded immunologically to higher haptoglobin levels. The discrepancy in  $\gamma$ -fraction values obtained by electrophoresis and immunodiffusion results from the fact that the  $\gamma$  fraction includes fast moving fractions such as  $\alpha$ - and  $\beta$ -globulins, when tested by immunodiffusion.

- 0771 STRUCTURAL DIFFERENCES IN THE HINGE REGION OF HUMAN GAMMA A MYELOMA PROTEINS OF DIFFERENT SUBCLASSES. (E.) Abel, C. A. (Natl. Jewish Hosp. Res. Ctr., Denver, Colo.) and H. M. Grey. *Nature* 233(35):29-31, 1971.

- 0772 THE MECHANISM OF DELAYED HYPERSENSITIVITY DERANGEMENTS IN RETICULUM CELL LYMPHOMATA (RETICULOSARCOMATA). (E.) Langner, A. (Warsaw Med. Acad., Poland), M. Pawinska-Proniewska and W. Glinski. *Brit J Derm* 85(1):1-6, 1971.

- 0773 IgM HEAVY CHAIN FRAGMENTS IN WALDENSTRÖM'S MACROGLOBULINEMIA. (E.) Bhooopalam, N. (U. Illinois Sch. Med., Chicago), B. M. Lee, V. J. Yakulis and P. Heller. *Arch Intern Med* 128:437-440, 1971.

- 0774 HISTOCHEMICAL AND HISTOIMMUNOLOGICAL INVESTIGATIONS OF NEURINOMA. (It.) Costanzi, G. (Sassari U., Italy), V. Eusebi, P. Muretto. *Riv Anat Pat Oncol* 35:136-149, 1969.

- 0775 ULTRASTRUCTURAL INVESTIGATIONS OF THE WISTAR RAT LYMPH NODE DURING TUMOR CELL INVASION. I. CELL REACTIONS TO SOLUBLE ANTIGENS. (Fr.) Puvion, F. (Inst. Cancer Res., Lille, France), G. Biserte, A. Clay and Y. Driessens. *C R Soc Biol (Paris)* 164 (12):2534-2538, 1971.

- 0776 HL-A ANTIGENS AND CHORIOCARCINOMA. (E.) Rudolph, R. H. (U. Washington, Sch. Med., Seattle) and E. D. Thomas. *Lancet* 2(7721):408-409, 1971.

- 0777 CELL PROLIFERATION IN THE PERITONEAL CAVITY I. PHYTOHEMAGGLUTIN-INDUCED PROLIFERATION OF MESOTHELIAL AND SUBMESOTHELIAL CONNECTIVE TISSUE, ENDOTHELIAL CELLS AND FREE CELLS FROM THE PERITONEAL FLUID. (Ger.) Mohr, W. (Ulm U., Germany), G. Beneke and L. Murr. *Beitr Path* 143(4):345-359, 1971.

- 0778 PECULIAR IMMUNOELECTROPHORETIC FINDINGS IN A CASE OF IgA-MYELOMA. (Ger.) Wiedermann, G. (Vienna U. Hygiene Inst., Austria), R. Maruna, H. Stemberger, F. Seidl and H. Matzenauer. *Wien Klin Wschr* 83(29/30):550-551, 1971.

- 0779 TYROSINASE FROM MALIGNANT MELANOMAS, NEVUS CELL NEVI AND CLINICALLY NORMAL SKIN: IMMUNOLOGICAL CHARACTERISTICS. (Ger.) Herrmann, W. P. (Köln U., Germany). *Arch Derm Forsch* 241:65-74, 1971.



0780 COMPARATIVE EFFECTIVENESS OF RESTORATION OF THE IMMUNE RESPONSE WITH ISOGENEIC BONE MARROW IN IRRADIATED AKR AND C57BL MICE. (E.) Umaly, R. (Radium Inst., Paris, France) and J. F. Duplan. *Rev Europ Etud Clin Biol* 16(6):582-585, 1971.

0783 IMMUNOGLOBULIN M BIOSYNTHESIS: PRODUCTION OF INTERMEDIATES AND EXCESS OF LIGHT-CHAIN IN MOUSE MYELOMA MOPC 104E. (E.) Parkhouse, R. M. E. (Natl. Inst. Med. Res., London, England). *Biochem J.* 123(4):635-641, 1971.

0781 REGRESSION OF BURKITT'S LYMPHOMA IN ASSOCIATION WITH MEASLES INFECTION. (E.) Bluming, A. Z. (Makerere U. Med. Sch., Kampala, Uganda) and J. L. Ziegler. *Lancet* 2(7715):105-106, 1971.

0784 LACK OF ANTIBODY ACTIVITY IN HUMAN MYELOMA PROTEINS. (E.) Yoo, T. J. (New York U. Med. Ctr., N.Y.) and E. C. Franklin. *J Immun* 167(2):365-367, 1971.

0782 CHANGES IN LYMPHORETICULAR TISSUES DURING GROWTH OF A MURINE ADENOCARCINOMA: I. HISTOLOGY AND WEIGHT OF LYMPH NODES, SPLEEN, AND THYMUS. (E.) Edwards, A. J. (St. Bartholomew's Hosp., London, England), M. R. Sumner, G. F. Rowland and C. M. Hurd. *J Nat Cancer Inst* 47(2):301-309, 1971.

See also:

- \* (Rev): 0601, 0602, 0606, 0608, 0612, 0626, 0627
- \* (Chem): 0637, 0665
- \* (Viral): 0694, 0700, 0708, 0712, 0717, 0722, 0724, 0740

- 0785 NUCLEAR DNA CONTENT IN HYPERPLASTIC LESIONS OF CYSTIC DISEASE OF THE BREAST WITH SPECIAL REFERENCE TO MALIGNANT ALTERATION. (E.) Izuo, M. (Dept. Path., Coll. Phys. Surg., Columbia U., New York, N.Y.), T. Okagaki, R. M. Richart and R. Lattes. *Cancer* 28(3):620-627, 1971.

Cystic disease of the breast was examined retrospectively using microspectrophotometry in a series of initial biopsies of patients for whom long-term follow-up data were available. The content and distribution of DNA in the nuclei of epithelial cells in hyperplastic lesions from patients with cystic disease of the breast was observed. Material included 15 lesions from 8 cases of cystic disease which later developed into carcinoma; these 15 lesions included 8 duct papillomatoses, 5 blunt duct adenoses, 1 sclerosing adenosis and 1 apocrine metaplasia. Another group of lesions came from patients who did not develop carcinoma. Three cases (comprising 5 lesions) from the group which developed carcinoma had an aneuploid nuclear DNA distribution pattern; 2 lesions had a hypodiploid stemline, 2 lesions were hyperdiploid and 1 lesion was near-diploid. In the other 5 cases which developed carcinoma the 10 observed lesions had typical diploid-to-tetraploid DNA distribution patterns. In the 7 cases of cystic disease which did not develop carcinoma, all lesions examined had a diploid-to-tetraploid DNA distribution.

- 0786 PATHOGENESIS OF CUTANEOUS MAREK'S DISEASE IN CHICKENS. (E.) Lapen, R. F. (Dept. Veterinary Sci., Washington State U., Pullman), S. G. Kenzy, R. C. Piper and J. M. Sharma. *J Nat Cancer Inst* 47(2):389-395, 1971.

Chronological changes in the distributional relationships between cutaneous immunofluorescent (IF) antigen and lymphoid aggregates, and in the development of cutaneous lymphoid aggregates, were investigated in chickens exposed to Marek's disease virus (MDV). Cutaneous sections from 55 MDV-exposed birds were examined for IF antigen. IF antigen was demonstrated in the cutaneous follicular epithelium, and MDV was isolated from chickens' blood, skin and kidneys, at the 10th but not at the 6th day after exposure to MDV. In subsequent chronological samples the frequency of birds positive for IF antigen and for evidence of MDV infection increased. In early samples, cutaneous IF antigen was generally limited to a few follicles per cutaneous section and to a few cells per follicle. In later samples, antigen was more widespread in the skin and in individual follicles, and was still present on the 45th day after MDV exposure. Chickens not exposed to MDV were always negative for cutaneous IF antigen, and MDV was not isolated from tissues of unexposed birds. IF antigen was in the skin before lymphoid aggregates; in all trials, cutaneous lymphoid aggregates were first observed in samples collected 13 days after MDV exposure. Lymphoid aggregates

were associated with IF antigen-positive sites in the overlying epidermis. In subsequent samples, the frequency of follicles positive for IF antigen alone decreased, reflecting an increased occurrence of lymphoid aggregates at antigen-positive sites. Cutaneous lymphoid aggregates changed from inflammatory to neoplastic-like lesions with time post exposure to MDV. Evidently, the gross cutaneous lymphoid lesions associated with Marek's disease arise from lymphoid aggregates which develop initially in response to MDV activity in feather follicle epithelium.

- 0787 STUDIES OF DORMANT TUMOR CELLS. (E.) Sugarbaker, E. V. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), A. S. Ketcham and A. M. Cohen. *Cancer* 28(3):545-552, 1971.

A study was designed to demonstrate the phenomenon of tumor cell dormancy using the Walker 256 tumor-Sprague-Dawley rat system. Rats were given sub-threshold doses of  $5 \times 10^3$ ,  $2.5 \times 10^4$  or  $1.25 \times 10^5$  Walker tumor cells intraportally, rats were subjected to laparotomy and liver massage when the liver was seen to be free of gross tumor, 4 or 12 wk after tumor cell injection. As many as 4 massages were performed, at 4 wk intervals. Seven of 40 rats given  $5 \times 10^3$  Walker tumor cells developed liver metastases following the first liver massage; ultimately, 85% of these rats developed metastases with multiple liver massages. Rats given  $1.25 \times 10^5$  tumor cells developed liver metastases in 92% of cases after liver massage, and rats given  $2.5 \times 10^4$  tumor cells developed liver metastases in 73% of cases following liver massage. None of the controls (rats given tumor cells but not given liver massage) developed liver metastases longer than the first 4 wk after inoculation. In rats given the first liver massage 12 wk after tumor cell injection, the growth of dormant cells in response to liver massage was significantly decreased as compared to rats given the first liver massage 4 wk after tumor cell inoculation. An attempt to demonstrate dormant cells in syngeneic Fisher rats using a benzo(a)pyrene-induced sarcoma was not successful. Although the benzo(a)pyrene-induced sarcoma was highly immunogenic in Fisher rats, the Walker tumor was apparently not immunogenic in Sprague-Dawley rats.

- 0788 CYTOPHOTOMETRIC STUDY OF PRECANCEROUS LESIONS OF THE FEMALE BREAST. (Ger.) Sachs, H. (Hamburg, U., Germany). *Beitr Path* 143(4):360-377, 1971.

DNA distribution patterns in precancerous, benign and malignant neoplastic tissues, as well as in physiologically altered specimens of the mammary gland from female patients, were established by means of



cytophotometric determinations. Histograms expressing semiquantitative data in work U (extinction x surface) of cellular DNA levels are given. Lactating breast as well as benign adenofibroma or cystic mastopathy revealed regular diploid DNA values of 6.4, 6.1, and 5.5 work U resp. Specific anomalous DNA stem lines were observed in samples from invasive carcinoma such as medullary adenocarcinoma and lactiferous duct carcinoma. However, lobular invasive carcinomas revealed normal diploid DNA values. Cytophotometric DNA determinations may prove to be useful in precancerous conditions for distinguishing between benign and malignant alterations of lactiferous ducts. However, the start of a malignant cell dedifferentiation process cannot be ascertained by quantitative histochemical DNA determinations alone. Additional parameters should be established in the future.

0789 RELATION BETWEEN URINARY ANDROGEN AND CORTICOID EXCRETION AND SUBSEQUENT BREAST CANCER. (E.) Bulbrook, R. D. (Imp. Cancer Res. Fund, London, England), J. L. Hayward and C. C. Spicer. *Lancet* 2(7721):395-398, 1971.

A study was carried out to test the hypothesis that abnormalities in the urinary excretion of androgen and corticosteroid metabolites preceded the clinical appearance of breast cancer. Urine specimens were collected from 5000 healthy women. When breast cancer was subsequently diagnosed in a woman taking part in the trial, her prediagnosis excretion of androgen and corticosteroid metabolites was compared with that of matched controls. The excretion of androsterone and etiocholanolone was found to be subnormal in 27 women who subsequently developed breast cancer. Low levels were found in women of all ages (within the range of 30-55 yr) and could be detected up to 9 yr before the appearance of the disease. Cancer patients and controls did not differ in their excretion of dehydroepiandrosterone and 17-hydroxycorticosteroid. It is suggested that androgen metabolite excretion might be considered suitable for screening a normal population for women with a high risk of breast cancer.

0790 CHROMOSOMES OF CANCER CELLS. (E.) Kirkland, J. A. (Queen Elizabeth Hosp., Woodville, South Australia) and M. A. Stanley. *Nature* 232(5313):632-633, 1971.

0791 FAMILIAL POLYPOSIS OF THE COLON: A FOUR-DECADE FOLLOW-UP. (E.) Sachatello, C. R. (U. Kentucky Med. Sch., Lexington). *Cancer* 28(3):581-587, 1971.

0792 RAT SERUM LIPOPROTEINS DURING CARCINOGENESIS OF THE LIVER IN THE PRENEOPLASTIC AND THE NEOPLASTIC STATE. (E.) Narayan, K. A. (Burnsides Res. Lab., U. Illinois, Urbana). *Int J Cancer* 8:61-70, 1971.

0793 BEHAVIOUR OF ADENYLIC ACID AND ADENOSINE DEAMINASE IN SPONTANEOUS MAMMARY CARCINOGENESIS IN MICE. (E.) Sheth, N. A. (Cancer Res. Inst., Tata Mem. Ctr., Bombay, India), S. V. Bhide and K. J. Ranadive. *Indian J Cancer* 7(4):274-279, 1970.

0794 ADENOCARCINOMA ARISING WITHIN CERVICAL ENDOMETRIOSIS AND INVADING THE ADJACENT VAGINA. (E.) Chang, S. H. (U. Alabama Med. Ctr., Birmingham) and W. A. Maddox. *Amer J Obstet Gynec* 110(7):1015-1016, 1971.

0795 WARTHIN'S TUMOR: A HYPERSENSITIVITY DISEASE?: ULTRASTRUCTURAL. LIGHT AND IMMUNOFLOUORESCENT STUDY. (E.) Allegra, S. R. (Tufts U. Sch. Med., Boston, Mass.). *Hum Path* 2(3):403-420, 1971.

0796 HISTOPATHOLOGICO-CLINICAL CORRELATION IN LYMPHOGRANULOMATOSIS. (E.) Jancina, J. (Slovak Oncol. Inst., Bratislava, Czechoslovakia), P. Kossey, J. Durkovsky and I. Kuzma. *Neoplasma* 18(4):407-412, 1971.

0797 ORAL CANDIDOSIS AND CARCINOMA. (E.) Eyre, J. (Inst. Dental Surg., U. London, England) and F. F. Nally. *Brit J Derm* 85:73-75, 1971.

0798 THE KARYOTYPE IN PRELEUKEMIC AND PRENEOPLASTIC CONDITIONS. (It.) Baserga, A. (Ferrara U., Italy). *Haematol Arch* 55(3):165-172, 1970.

- 0799 CANINE MAMMARY TUMORS. (E.) Moulton, J. E. (Sch. Veterinary Med., U. California, Davis), D. O. N. Taylor, C. R. Dorn and A. C. Anderson. *Path Vet* 7:289-320, 1971.
- 0800 CLINICAL AND ANATOMICAL-PATHOLOGICAL CONSIDERATIONS ON THE MALIGNANT TRANSFORMATION OF GASTRIC ULCER. (Fr.) Kourias, B. G. (Red Cross Hosp., Athens, Greece) and N. Papacharalampous. *Arch Fran Mal Appar Dig* 60(6-7):309-318, 1971.
- 0801 COLONIC AND RECTAL POLYPS IN ADULTS. (Fr.) Vignal, J. (Edouard-Herriot Hosp., Lyon, France). *Ann Chir* 25(11-12):606-608, 1971.
- 0802 CHILDHOOD RECTAL AND COLONIC POLYPS DIAGNOSED AS SOLITARY: DISCUSSION OF 700 CASES. (Fr.) Duhamel, J. (Paris, France) and N.-Q. Binh. *Ann Chir* 25(11-12):615-617, 1971.
- 0803 BRONCHOGENIC CARCINOMA: ANATOMICAL AND PHYSIOLOGICAL CONDITIONS OF ITS ORIGIN AND EVOLUTION: III. STUDY OF GROWTH AND EVOLUTIONARY DYNAMIC OF BRONCHOGENIC CARCINOMA. ITS SIGNIFICANCE FOR DIAGNOSIS. (E.) Mucholda, F. (Fac. Med., Charles U., Prague, Czechoslovakia), Z. Borek and L. Lhotka. *Acta Univ Carol [Med]* Monograph 41:39-62, 1970.
- 0804 CONSIDERATIONS ON COLON AND RECTUM POLYPOSIS. (Fr.) Deminatti, M. (Lille Med Sch., France). *Ann Chir* 25(11/12):591-593, 1971.
- See also:
- \* (Rev): 0605, 0628, 0629
  - \* (Chem): 0666, 0669
  - \* (Viral): 0720
  - \* (Epid-Biom): 0810



0805 TIME TRENDS OF INTESTINAL AND DIFFUSE TYPES OF GASTRIC CANCER IN NORWAY. (E.) Munoz, N. (Int. Agency Res. Cancer, Lyons, France) and J. Asvall. *Int J Cancer* 8:144-157, 1971.

Time trends for the 2 main histologic types of gastric cancer were investigated in Norway; tissue samples of gastric cancer were diagnosed as "intestinal" (i.e., well-differentiated adenocarcinoma), "diffuse" (i.e., undifferentiated adenocarcinoma), or "other". Samples of these types of gastric cancer were drawn from the periods 1940-1944 (I), 1952-1953 (II) and 1960-1964 (III). In period I the intestinal type of gastric cancer was most frequent, accounting for 51.3% of gastric cancer cases in all age groups; diffuse gastric cancer accounted for 39.7% of gastric cancer cases in this period. No difference in this distribution was found between I and II. However, between II and III there was a marked change in the relative frequency of the intestinal and diffuse types, with the former decreasing to make up 35.6% of all gastric cancer cases and the latter increasing to make up 54.2% of all cases. In both sexes the intestinal type was relatively more frequent in the younger age groups. The decline in the intestinal type observed from II to III was greater for females than for males, and it was more pronounced in the under-50-yr-old age group. The gastric cancer death rates in Norway were also examined; it was found that, for both sexes, mortality from gastric cancer fell from the early 1930's to the middle 1960's but that this decline stopped temporarily during the latter half of the 1940's. The general decline in gastric cancer mortality and its interruption in the latter part of the 1940's may be related to dietary factors, specifically to an increase in cereal intake and/or a decrease in the intake of fats, especially milk fats. Dietary changes in Norway brought about by the Second World War may have halted the decline in gastric cancer mortality in period I. Dietary factors influencing the gastric cancer death rate were thought primarily to affect the intestinal type of gastric cancer.

0806 TIME TRENDS OF INTESTINAL AND DIFFUSE TYPES OF GASTRIC CANCER IN THE UNITED STATES. (E.) Munoz, N. (Int. Agency Res. Cancer, Lyons, France) and R. Connelly. *Int J Cancer* 8:158-164, 1971.

The relationship between the observed decline in incidence of gastric cancer in the United States during the last 40 yr and the incidence of the 2 main histologic types of gastric cancer was investigated. All histologically confirmed gastric cancer cases diagnosed during the periods 1940-1944 and 1960-1964 at the Hartford (Connecticut) Hospital were classified into 3 groups: "intestinal" (i.e., well-differentiated adenocarcinoma), "diffuse" (i.e., undifferentiated carcinoma), and "other". There were 62 native-born and 65 foreign-born cases; cases were subdivided into high- or low-risk groups

according to the risk for gastric cancer prevailing in the patients' birthplaces. High-risk areas included Western Europe, U.S.S.R. and Poland, China and South America, and low-risk areas included the United States, Canada, Greece and South Africa. Thirty-nine cases of gastric cancer were diagnosed during 1940-1944 and 88 cases were diagnosed during 1960-1964. Seventy-four cases were classified as intestinal type, 45 as diffuse type and 8 as other types. Intestinal-type tumors were most prominent in persons from high-risk areas. The percentage of intestinal-type cases appeared to have decreased between 1940-1944 and 1960-1964. For the combined male and female sample, 69.2% of cases were of the intestinal type in 1940-1944 and 53.4% of cases were of the intestinal type in 1960-1964. Although this decrease was not statistically significant, it persisted within each sex and risk group category (with the exception of the low-risk female group). The predominance of the intestinal-type of gastric cancer was more noticeable among female than among male cases. The findings suggested that intestinal and diffuse gastric cancer differ etiologically as well as structurally and epidemiologically.

0807 A GEO-PATHOLOGICAL STUDY OF MALIGNANT MELANOMA IN JAPAN. (E.) Mori, W. (Tokyo Med. Dent. Coll., Japan). *Path Microbiol* 37:169-180, 1971.

Epidemiological features of malignant melanoma in Japan were studied in a survey of 212 autopsies of malignant melanoma performed during 1958-1967. The general incidence of malignant melanoma was 0.16% of all autopsies during this 10-yr period; 131 cases were males (61.8%). The highest incidence of malignant melanoma was seen in the 50-69-yr-old age group. To determine the regional differences in malignant melanoma in Japan, the country was divided into 5 districts: A, Hokkaido (northern Japan); B, Akita, Aomori, etc. (north-central Japan); C, Kyoto, Tokyo, etc. (South central Japan); D, Ehime, Hiroshima, etc. (southern Japan); and E, Fukuoka, Kagoshima, etc. (extreme southern Japan). In districts A and B, the incidence of malignant melanoma among all autopsies was 0.24 and 0.25%, resp., in C and D, the incidence was 0.14 and 0.14%, resp., and E the incidence was 0.10%. All major groups of malignant melanoma, but especially tumors of central-nervous and ocular origin, had a higher incidence in the northern districts. Cutaneous neoplasms made up 52% of all melanomas; half of these lesions originated in the lower extremities, the sole of the foot being one predisposed site. The conclusion that areas of the body exposed to sunlight are sites of predilection was not supported by these findings, and the higher incidence of melanoma in the less sunny areas of Japan suggested that the role of sunlight in the causation of melanoma remains an undecided issue. A high incidence of

mucosal melanomas, including melanomas of the oral, nasal and paranasal cavities, was found; oral cavity melanoma was more common among females than males (10 female cases versus 4 male cases).

- 0808 EPIDEMIOLOGIC FEATURES OF BREAST CANCER IN SLOVENIA, 1965-1967. (E.) Ravnihar, B. (Med. Fac., U. Ljubljana, Yugoslavia), B. Macmahon and J. Lindtner. *Eur J Cancer* 7:295-306, 1971.

In the course of a study of the incidence patterns of breast cancer among females in Slovenia (Yugoslavia) conducted between October 1964 and December 1967, 772 breast cancer patients were interviewed; patients were compared with a total of 2308 interviewed non-breast cancer patients (controls). The age-specific incidence of breast cancer in Slovenia was similar to that in Athens; in the 65-yr-old age group there were 80 cases of breast cancer/100,000 population/yr in Slovenia and 90 cases/100,000 population/yr in Athens. The incidence rate for breast cancer was about half the rate in Boston; in Boston there were 175 breast cancer cases/100,000 population/yr in the 65-yr-old age group. There were no significant differences between Slovenian cases and controls in socio-economic status, a finding which ran counter to findings in other areas, where a tendency has been found for breast cancer patients to be of high socio-economic status. However, it was thought that the same economic differential in breast cancer risk that has been seen elsewhere existed in Slovenia, masked in the present study by differences in the sources of cases and controls. No significant differences between Slovenian cases and controls were found in the number of fetal deaths or in frequency or duration of lactation. In Slovenia, the risk of developing breast cancer among women having borne 5 or more children was 85% of the risk incurred by nulliparous women. Women first becoming pregnant under the age of 25-yr-old had about 70% of the breast cancer risk of women whose first pregnancy was delayed until 30-yr-old or older; thus, the protective effect of early pregnancy seemed substantially less in Slovenia than in other areas studied. There was a distinct trend towards higher breast cancer risk with earlier age at menarche. An indication that late menopause was associated with increased breast cancer risk was also found. Breast cancer patients were significantly taller and heavier than the controls.

- 0809 RATES PER 100,000 BIRTHS AND INCIDENCE OF CHORIOCARCINOMA AND MALIGNANT MOLE IN SINGAPORE CHINESE AND MALAYS: COMPARISON WITH CONNECTICUT, NORWAY AND SWEDEN. (E.) Shanmugaratnam, K. (Gen. Hosp., Singapore), C. S. Muir, S. H. Tow, W. C. Cheng, B. Christine and E. Pedersen. *Int J Cancer* 8:165-175, 1971.

Age-adjusted incidence rates for malignant trophoblastic neoplasia (MTN), choriocarcinoma (CC) and malignant mole (MM) were determined for Chinese and Malay inhabitants of Singapore; rates were compared to rates for Americans and Scandinavians. Case material was collected in Singapore between 1959-1964. The age-standardized rates for MTN, CC and MM among Singapore Chinese were 1.45, 1.00 and 0.45 cases/100,000 population per annum resp. Rates for MTN, CC and MM among Singapore Malays were higher: 2.14, 1.17 and 0.97 cases/100,000 per annum resp. The impression that rates for MTN, CC and MM were higher in the Far East than in Western nations was confirmed. The age-standardized rates for MTN, CC and MM among Norwegians (1957-1966) were 0.22, 0.19 and 0.03 cases/100,000 per annum resp., and the rates for MTN, CC and MM among Connecticut residents (1935-1964) were 0.09, 0.07 and 0.02 cases/100,000 per annum resp. The rate for histologically diagnosed MTN/100,000 live births and still births was 18 for both Singapore Chinese and Singapore Malays. Both Chinese and Malay women showed a considerable increase in risk for MTN with advancing age; this increase may reflect effects of increasing parity rather than effects of aging.

- 0810 THE INCIDENCE OF FIBROCYSTIC MASTOPATHY AND OF UTERINE FIBROMA IN AN APPARENTLY HEALTHY POPULATION SAMPLE. (It.) Caruso, C. (Regina Elena Inst. Tumor Res. Ther., Rome, Italy). M. Casciulli, A. Cavallari, A. Salvati, E. Schinina. *Minerva Ginec* 23(9):440-442, 1971.

The incidence of fibrocystic mastopathy and uterine fibroma was studied in a population sample of 3,337 women who were subjected to oncological control between 1967 and 1969 and had no evident pathological symptoms. A high percentage (20%) among the direct relatives of these women had had neoplasia. Uterine fibroma was ascertained in 282 of the examined 3,337 women, an 8% incidence. Of these, 139 cases were detected in women between 40 and 55 yr-of-age, while a peak incidence in fibroma was found among the 45-50-yr-of-age group. Major incidence of uterine fibroma was encountered among nulliparous women or among women who had less than 3 pregnancies in their past history. An alteration of the ovarian function was considered to be a contributing factor in both conditions. Mastopathy was detected in 1,213 women of this population group and 127 of these women (3% with respect to the whole population) had both diseases in association. Major incidence of associated mastopathy and fibroma was found among the 45-50 yr-old group. A common hormonal etiological factor for both mastopathy and uterine fibroma is assumed in an attempt to interpret the high incidence of their associated occurrence.

- 0811 TIME-SPACE CLUSTERING OF CHILDHOOD LEUKEMIA IN NEW ZEALAND. (E.) Glass, A. G.



(Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), N. Mantel, F. W. Gunz, and G. F. S. Spears. *J Nat Cancer Inst* 47(2):329-336, 1971.

Two independent statistical procedures, developed, respectively, by Knox and Mantel, were used to analyze data on time-space clustering of leukemia among children under 15-yr-old in New Zealand. The date of diagnosis of leukemia and the home address of the subject were the time and space co-ordinates used in the 2 statistical analyses. Findings confirmed time-space clustering of leukemia in New Zealand. The clustering was most significant at close time-space separations (Knox method) or small additive constants (Mantel method) and was particularly evident at space separations of less than 2 miles and at time separations of less than 3 mo. Clustering tended to be most significant for children under 6-yr-old at onset of leukemia; both statistical methods also indicated clustering for the 0-14-yr-old age group. Clustering was relatively weak when the youngest and oldest children were eliminated from consideration. It appeared that, if an environmental agent was active in the etiology of leukemia, it was detectable only in very early life. Because the sample was derived over a 12-yr period, it seemed possible that major population shifts in New Zealand might have played an unpredictable role in the clustering analysis.

0812      RETINOBLASTOMA: EPIDEMIOLOGIC CHARACTERISTICS. (E.) Jensen, R. D. (Natl. Cancer Inst., Natl. Inst. Hlth. Bethesda, Md.) and R. W. Miller. *New Eng J Med* 285(6):307-311, 1971.

A survey of 269 fatalities among children with retinoblastoma showed mortality from retinoblastoma was equal for each sex. The number of deaths among Caucasian children under 15-yr-old was 67 and there were 196 deaths among Negro children. The annual mortality rate for Negro children from retinoblastoma was 42.5 deaths/million population among children aged 2-3-yr-old, while the annual mortality rate for Caucasian children of the same ages was 17 deaths/million. A survey of 1623 hospital records of children with retinoblastoma revealed that among Caucasian children the frequency of retinoblastoma by age at diagnosis declined steeply from a peak in infancy. By contrast, among Negroes fewer diagnoses were made during the first year of life, and more diagnoses were made from 1-4 yr of age. No clustering of retinoblastoma mortality was found in any one area of the United States, and in no family did more than one sib die of retinoblastoma between 1960-1967. Fifty-three of 1077 children with retinoblastoma were found to have major congenital malformations. An excess of mental retardation was found in the patients; 15 cases of mental retardation were observed among retinoblastoma patients, whereas the expected number of cases of retardation was 4.7. Other malformations, such as eczema, microcephaly, colobomas, malformed ears and cleft palate, occurring in children

with retinoblastoma, were associated with D-deletion syndrome. Radiotherapy in the retinoblastoma patient group was found to be associated with excesses of osteosarcoma, soft-tissue sarcoma and skin carcinoma. The number of primary cancers other than retinoblastoma occurring in the retinoblastoma patients seemed to exceed expectation; 11 children with retinoblastoma were found to have second primary tumors, including 3 with osteosarcoma, thus suggesting an innate susceptibility that may add to the risk of radiotherapy.

0813      COMPARISON OF LUNG CANCER MORBIDITY AND MORTALITY IN SWEDEN: 1959-1966. (E.) Larsson, S. (Sahlgren's Hosp., U. Gothenburg, Sweden). *Acta Path Microbiol Scand A*(79):524-528, 1971.

Lung cancer incidence and mortality in Sweden for the period 1959-1966 were compared. The incidence of lung cancers specified as primary or not otherwise specified was higher than the corresponding mortality, and the difference between incidence and mortality increased towards the end of the 8-yr sample period. The difference was especially pronounced in the under-70-yr-old age group. Although it was noted that epidermoid lung carcinoma has a more favorable prognosis than anaplastic lung carcinoma, a preponderance of one histological type of cancer did not account for the divergence of incidence and mortality, for the distribution of histological types of lung cancer did not differ significantly in the patients. The difference between recorded incidence and mortality seemed to be the result of effective therapy (especially surgical therapy) in younger age groups.

0814      CANCER IN EAST AFRICAN INDIANS. (E.) Chopra, S. (Aga Khan Platinum Jubilee Hosp., Nairobi, Kenya) and A. C. Templeton. *Int J Cancer* 8:176-183, 1971.

The incidence of carcinoma of various sites among Indians resident in East Africa (Kenya and Uganda) was compared with the incidence of carcinoma among Indians in 2 other regions: South Africa (Durban) and India. A total of 586 cases of cancer in East African Indians was surveyed. The overall incidence of carcinoma in Ugandan Indians was 28.9 cases/100,000 population for males and 30.4 cases/100,000 population for females. The incidence of mammary carcinoma among East African Indians was far higher than among Indians in Durban or India; in Africa, Muslim Indian women had a higher rate for mammary carcinoma than Hindu Indian women. Gastric and bronchial neoplasms, relatively common in Durban, were less common in East Africa. Oral tumors were more common among Indians in India than among Indians in either East or South Africa. Lymphoreticular tumors were more common among Indians in East Africa than among Indians in Durban or India. In most cases

the differences in the incidence of cancer of various sites in Indians living in the 3 regions investigated were explicable in terms of environmental factors.

- 0815 A CONTRIBUTION TO THE STUDY OF POST-PREGNANCY TROPHOBLASTOMA. TUMOR DOUBLING TIME AND THE PROLAN TEST. (Fr.) Hinglais, H. (Paris, France) and M. Hinglais. *C R Acad Sci [D] (Paris)* 273(2):263-265, 1971.
- 0816 HEREDITY AND ONCOGENESIS IN CHILDHOOD. (E.) Innis, M. D. (Princess Alexandra Hosp., Brisbane, Australia). *Oncology* 25(2):183-187, 1971.
- 0817 BOVINE LEUKOSIS, HUMAN LEUKEMIA AND RELATED DISEASES: AN EPIDEMIOLOGICAL INVESTIGATION FROM 1957-1962, DANISH RECORDS. (Dan.) Henriksen, E. (No affiliation) and P. B. Jensen. *Ugeskr Laeg* 133(25):1201-1205, 1971.
- 0818 INCREASING THYROID CANCER IN OHIO 1968 THROUGH 1970. (E.) Sinkey, J. R. (Med. Coll. Ohio, Toledo). *Ohio Med J* 67(9):816-817, 1971.
- 0819 REGIONAL PATTERNS IN MORBIDITY FROM MELANOMA IN TEXAS 1944-1966. (E.) Macdonald, E. J. (U. Texas M. D. Anderson Hosp., Houston), M. S. Johnson and A. Murphy. *Cancer Bull* 23(3):51-55, 1971.
- 0820 CARCINOMA OF THE PALATE IN VISAKHAPATNAM AREA. (E.) Reddy, C. R. R. M. (Andhra Med. Coll., Visakhapatnam, India), V. R. Kameswari and M. V. S. Raju. *Indian J Cancer* 8(2):84-91, 1971.
- 0821 CANCERS OF THE GENITO-URINARY SYSTEM IN THE DAKAR, AFRICA, AREA. (Fr.) Tossou, H. (No affiliation), A. Mensah and S. Sylla. *Med Afrique Noire* 18(5):441-447, 1971.
- 0822 INCIDENCE OF NASOPHARYNGEAL CANCER IN HONG KONG: A REPORT. (E.) Ho, H. C. (Hong Kong). *UICC Bull* 9(2):5, 1971.
- 0823 CANCERS IN AFRICAN CHILDREN IN SENEGAL. (Fr.) Dan, V. (Fac. Med., U. Dakar, Senegal), I. Niang and G. Senghor. *Med Afrique Noire* 18(5):407-422, 1971.
- 0824 CANCERS OF THE RESPIRATORY SYSTEM: I. PRIMARY CANCERS. (Fr.) Chataigneau, P. (No affiliation) and M. Rabier. *Med Afrique Noire* 18(5):425-430, 1971.
- 0825 SECONDARY CANCERS OF THE LUNG IN DAKAR. (Fr.) Sankale, M. (Med. Clin., Dakar, Senegal), B. Diop, P. A. Kane, P. N'Diaye, N. Diallo and N. Kuakuvi. *Med Afrique Noire* 18(5):433-438, 1971.
- 0826 INCIDENCE AND DISTRIBUTION OF ACUTE LEUKAEMIA IN ONE DISTRICT GENERAL HOSPITAL AREA. (E.) Powell, D. E. B. (Gen. Hosp., Bridgend, Glamorgan, Wales). *Lancet* 3(7720):350-351, 1971.
- 0827 PRIMARY CARCINOMA OF THE LIVER IN BOMBAY. (E.) Patwardhan, J. R. (Grant Med. Coll., Bombay, India), V. H. Kshirsagar and R. K. Gadgh. *Indian J Cancer* 7(2):113-118, 1970.
- 0828 APPLICATION OF A MATHEMATICAL MODEL TO A CLINICAL STUDY OF THE LOCAL SPREAD OF ENDOMETRIAL CANCER. (E.) Blumenson, L. E. (Roswell Park Mem. Inst., Buffalo, N.Y.), I. D. J. Bross and N. H. Slack. *Cancer* 28(3):735-744, 1971.

See also:

- \* (Rev): 0610, 0621  
\* (Chem): 0645



# MISCELLANEOUS

- 0829 SELECTIVE AGGREGATION OF L1210 LEUKEMIA CELLS BY THE POLYCATION CHITOSAN. (E.)  
Sirica, A. E. (Microbiol. Assoc., Inc., Bethesda, Md.) and R. J. Woodman. *J Nat Cancer Inst* 47(2):377-386, 1971.

The ability of the polycation chitosan selectively to aggregate murine ascites tumor cell types was compared to the ability of chitosan to aggregate normal murine erythrocytes and bone marrow cells. Chitosan aggregated L1210 leukemia ascites cells (from DBA/2 mice) at a concentration ( $0.006 \times 10^{-3}$  mEq/ml) nearly 10 times lower than the concentration required to aggregate normal erythrocytes and bone marrow cells. Two other polymers, poly-L-lysine and polyethylenimine, aggregated L1210 cells at the same low concentration as chitosan, but in contrast to chitosan, they produced the same effect against erythrocytes. Neither chitosan nor poly-L-lysine nor polyethylenimine selectively aggregated Sarcoma 37 or Ehrlich ascites cells as compared with normal cells. After 30 min of exposure, poly-L-lysine produced, in addition to dense aggregation, cytoplasmic swelling, membrane distortion of erythrocytes, and hemolysis. Chitosan produced only slight aggregation of erythrocytes, and did not significantly alter the morphology of the erythrocytes. Fifty percent of L1210 cells became permeable to trypan blue when incubated with  $0.4 \times 10^{-3}$  mEq/ml poly-L-lysine or with  $0.8-1.6 \times 10^{-3}$  mEq/ml chitosan. Incubation of L1210 cells with chitosan or poly-L-lysine partially inhibited the transplantability of cells as measured by survival time, after inoculation with L1210 cells, of (C57BL x DBA)F<sub>1</sub> (BDF<sub>1</sub>) mice. Immunosuppression with 180 mg/kg cyclophosphamide did not significantly alter this effect, and chronic chitosan treatment of mice which bore i.p. implants of L1210 cells retarded the dissemination of the leukemic cells into peripheral blood.

- 0830 ESTROGEN INHIBITION OF MAMMARY TUMOR GROWTH IN RATS: COUNTERACTION BY PROLACTIN. (E.)  
Meites, J. (Dept. Path., Michigan State U., East Lansing), E. Cassell and J. Clark. *Proc Soc Exp Biol Med* 137(4):1225-1227, 1971.

Experiments were designed to determine whether estrogen-induced inhibition of growth of established mammary adenocarcinoma in rats could be overcome by administration of prolactin. Female rats were given a single i.v. injection of 7,12-dimethylbenz(a)anthracene; 3 mo. later, when most rats had developed mammary tumors, tumor-bearing rats were divided into 3 groups and treated as follows: (1.) daily s.c. injections of corn oil (controls); (2.) daily s.c. injection of 20 µg estradiol benzoate (EB); (3.) 20 µg EB and 1 mg prolactin injected daily. Controls showed an average gain in number of tumors from 2.4 to 3.4 by 20 days, and an increase in mean total tumor diameter/rat from 7.0 to 10.7 cm. By contrast, rats given EB showed a loss in average number of tumors/rat from 2.5 to 1.7 and a slight but insignificant reduction

in average total tumor diameter from 13.1 to 12.6 cm. Rats given both EB and prolactin showed a significant gain in mean total tumor diameter from 9.5 to 14.2 cm and a slight but insignificant gain in total number of tumors/rat. Results suggested that a large dose of estrogen interfered with the peripheral stimulatory action of prolactin on mammary tumor tissue.

- 0831 AUTOREGULATION OF ASCITES TUMOUR GROWTH BY INHIBITION OF THE G-1 AND THE G-2 PHASE. (E.) Bichel, P. (Danish Cancer Society, Aarhus). *Europ J Cancer* 7:349-355, 1971.

Inhibition of recurrent growth of a mouse ascites tumor by injection of cell free ascites fluid was investigated; the ascites tumor employed was a hypotetraploid plasmacytoma JB-1 in AK strain mice. Mice bearing tumors were injected i.p. with ascites fluid and Colcemid; the accumulation of mitotic cells was followed for the next 5 hr. During the first 2.5 hr after injection, the mitotic index in treated mice was the same as that in controls; for the following 1.5 hr there was a complete cessation in the admission of cells to the mitotic phase, indicating that a blockage in the mitotic cycle had taken place about 2.5 hr before the midpoint of the mitotic phase. Four hr after the injection of cell free ascites a burst of mitotic cells was seen, indicating that the inhibition of tumor cells was only temporary. It appeared that the blockage was localized at the beginning of the G-2 period, or at the boundary between S and G-2. A complete but temporary blockage was also found to affect cells in the G-1 phase. An auto-regulation mechanism operating in the growth of ascites tumors was suggested by these findings; this autoregulation may be similar to the homeostatic growth regulation of some normal tissues.

- 0832 TUMOR PRODUCTION IN IMMUNE-SUPPRESSED HAMSTERS BY SPONTANEOUSLY TRANSFORMED HUMAN PROSTATIC EPITHELIUM. (E.) Fraley, E. E. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and S. Ecker. *J Urol* 106:95-99, 1971.

A human prostatic adenoma was established in tissue culture where it grew as epithelial cells; after more than 200 passages *in vitro* the growth rate for the adenoma epithelial cells was rapid in monolayer and suspension cultures. The prostatic adenoma cells appeared malignant and morphologically bizarre; tumor cells from the 24th passage had a modal chromosome number of 64. Adenoma cells had a well-developed rough endoplasmic reticulum, many

microvilli and desmosomes. Suspensions containing  $10^6$ - $10^7$  tumor cells were injected into the cheek pouches of neonatal hamsters; recipients had been exposed to 500 R of irradiation. Small tumors appeared in inoculated hamsters after 7 days post-inoculation; the tumors were anaplastic and invaded surrounding connective tissue. Inoculated hamsters which received no further immunosuppression successfully rejected the tumors induced by prostatic adenoma cells within 2 wk postinoculation. No Mycoplasma were detectable in prostatic adenoma cell cultures.

0833 EFFECT OF FLUPHENAZINE HCl ON R3230AC MAMMARY CARCINOMA AND MAMMARY GLANDS OF THE RAT. (E.) Hilf, R. (Squibb Inst. Med. Res., New Brunswick, N. J.), C. Bell, H. Goldenberg and I. Michel. *Cancer Res* 31(8):1111-1117, 1971.

Female rats were given axillary transplants of the R3230AC mammary carcinoma prior to the s.c. injection of fluphenazine hydrochloride. Administration of the phenothiazine drug stimulated normal mammary glands and inhibited growth of mammary tumor. Administration of 12.5, 25.0 or 50 mg/kg/day of fluphenazine hydrochloride to tumor-bearing rats resulted in decrease in tumor weight by 49, 31 and 38% resp. Fluphenazine hydrochloride caused a dose-related decrease in DNA content in carcinoma cells; DNA concentration in tumor tissue of rats given no fluphenazine hydrochloride was 7.66  $\mu$ g/mg while DNA concentration in tumor tissue of rats given 50 mg/kg/day of tranquilizer was 5.99  $\mu$ g/mg. Cholesterol levels in tumor tissue were reduced after fluphenazine treatment and increased levels of free fatty tissue of treated rats. Fluphenazine caused increases in glucose 6-phosphatase dehydrogenase and NADP-malate dehydrogenase activity in tumor tissue. Decreases in the activity of NADP-isocitrate dehydrogenase, glucosephosphate isomerase,  $\alpha$ -glycerolphosphate dehydrogenase, pyruvate kinase, hexokinase and glucokinase were seen in tumors of rats given fluphenazine. DNA concentrations in mammary gland tissue of tumor-bearing rats were reduced by fluphenazine; cholesterol and free fatty acids were also reduced in mammary glands of tumor-bearing rats given fluphenazine. Marked increases in enzyme activity levels were seen in mammary tissue of treated rats.

0834 IMPAIRED PROCESSING OF RIBOSOMAL PRECURSOR RNA IN BLAST CELLS OF ACUTE LEUKEMIA. (E.) Torelli, U. L. (Inst. Med. Path., U. Modena, Italy), G. M. Torelli, A. Andreoli and C. Mauri. *Acta Haemat* 45:201-208, 1971.

Blood from 9 patients with acute leukemia was sedimented and 6 blast cells were incubated with  $^3$ H-

5-uridine and  $^{14}$ C-methyl-methionine for periods of 30 min to 6 hr; after incubation, RNA was separated and analyzed by sedimentation in sucrose gradients. 45S RNA was in all cases the molecule associated with the largest radioactive peak in the sedimentation profile after 1 hr of incubation with labeled precursor; the 45S RNA molecule was evidently of ribosomal precursor nature. In all cases,  $^3$ H-uridine radioactivity in the 45S-32S fractions remained the predominant portion, while radioactivity from  $^{14}$ C-methyl-methionine was transferred, over a period of 5-6 hr, from the 32S-45S region to the 18S-28S region. In contrast to normal proliferating blood cells, the methylation and cleavage of 45S precursor RNA in leukemic blasts occurred at a very low rate. The rate of formation of 18S RNA in blood cells from different leukemia patients differed greatly. An accumulation of unmethylated labeled RNA molecules in the size range of ribosomal precursor RNA was seen; this suggested that circulating leukemic blast cells are characterized by unbalance between processing of ribosomal precursor RNA and rate of synthesis, causing an accumulation of methylated precursor.

0835 EFFECTS OF SOLUBLE FACTORS FROM LYMPHOCYTES ON ONCOGENESIS IN MAN. (Fr.) May-Levin, F. (Gustave-Roussy Inst., Villejuif, France), G. Graffte and G. Brule. *C R Acad Sci [D] (Paris)* 272(23): 2996-2999, 1971.

Known cytotoxic factors can be released from lymphocytes *in vitro* after stimulation. These soluble elements were applied in an attempt to check the growth of human tumors in refractory cases. Lymphocytes were cultured by 3 different methods: method "A" using lymphocytes obtained from 2 healthy subjects; method "B" using equal numbers of lymphocytes from the patient to be treated and from a normal subject; and method "C" using a cytotoxic factor of actual tumoral cells. The nonspecific method (method A) was applied in 13 subjects (all with skin metastases), 11 of whom had a primary mammary adenocarcinoma and 2 of whom had a diffuse melanocarcinoma. The superficial lesions remained unchanged but the subcutaneous nodules regressed; in one patient as many as 9 nodules disappeared. The deep lesions in these patients, however, continued to develop. Using the cultures obtained from the other 2 methods, the regression of the cutaneous lesions began with the first injection. Preliminary results demonstrate the possibility of obtaining an antitumoral action by means of certain biological factors released by cultured lymphocytes following stimulation.

0836 DISTINGUISHING BETWEEN THE CHROMOSOMES INVOLVED IN DOWN'S SYNDROME (TRISOMY 21) AND CHRONIC MYELOID LEUKAEMIA ( $Ph^1$ ) BY FLUORESCENCE. (E.) O'Riordan, M. L. (Western Gen. Hosp., Edin-



burgh, Scotland), J. A. Robinson, K. E. Buckton and H. J. Evans. *Obstet Gynec Survey* 26(9):647-648, 1971.

Chromosome preparations were made from peripheral blood of 10 patients with Down's syndrome and from 4 patients with chronic myeloid leukemia. It was found that in all 10 Down's syndrome patients the extra G group chromosome (number 21) belonged to the shorter pair with a strongly fluorescent band in the proximal region of the long arms. Blood cells from leukemic patients were observed with and without stimulation by phytohemagglutinin (PHA). In PHA-stimulated leukocytes 4 G group autosomes were seen with the standard normal fluorescence pattern of normal cells. In PHA-stimulated leukemic cells possessing the distinctive  $Ph^1$  chromosome, and in stimulated mitotic cells, the deleted G group chromosome was in all cases a member of the weakly fluorescent chromosome pair. Apparently, the trisomic G chromosome in Down's syndrome blood samples, designated chromosome 21, is the G chromosome with a distinctive fluorescent band; the deleted G chromosome (designated  $Ph^1$ ) in chronic myeloid leukemia, however, appears to be a member of the weakly fluorescing pair and must therefore be chromosome 22.

0837 RADIATION EFFECTS ON MACROMOLECULAR SYNTHESIS IN CONTACT INHIBITION-SENSITIVE CELLS SYNCHRONIZED BY MEDIUM CHANGE. (E.) Yoshikura, H. (Radium Inst., Orsay, France). *Radiat Res* 47(2): 548-561, 1971.

A line of newborn C3H/He mouse kidney cells, established in culture, stopped growing after logarithmic growth; when culture medium was changed, cells divided in a synchronized fashion once. DNA synthesis began to increase 10 hr after medium change and reached its maximum at 20 hr; mitosis occurred 10 hr later than DNA synthesis. There were 2 peaks of RNA synthesis: one just after medium change and the other just before the DNA peak. Stimulation of protein synthesis followed RNA synthesis. The cells were irradiated with UV at doses of 50 and 100 ergs/mm<sup>2</sup> 3 or 21 hr after medium change; irradiation at 3 hr inhibited DNA synthesis to 20 and 10% of maximum, while irradiation in the middle S phase inhibited <sup>3</sup>H-thymidine incorporation to 60 and 40% of maximum. G<sub>1</sub> phase irradiation inhibited DNA synthesis more strongly than S phase irradiation. The cells were irradiated with γ-rays from <sup>60</sup>Co at 1070 R 4 or 19 hr after medium change; irradiation at 4 hr after medium change inhibited DNA synthesis to 50% of maximum while irradiation in the S-phase reduced DNA synthesis by less than 10%. Thus, DNA synthesis was inhibited more strongly when cells were irradiated before the onset of DNA synthesis than when cells were irradiated during DNA synthesis. Irradiation by UV immediately inhibited RNA synthesis stimulated by medium change. Protein synthesis which followed RNA synthesis was more strongly inhibited when the cells were irradi-

ated before induction of RNA synthesis than when cells were irradiated after induction of RNA synthesis. γ-ray irradiation to 25 kR did not affect protein synthesis; at 30 kR of γ-rays protein synthesis decreased slightly.

0838 A STUDY ON HORMONE DEPENDENCY OF BREAST CANCER. (E.) Yogo, H. (Nagoya U. Sch. Med., Japan), T. Sasaki, T. Yamaoka, K. Matsuoka, H. Negoro and T. Goto. *Nagoya J Med Sci* 34:79-87, 1971.

Sex hormone dependency of breast cancer was studied *in vitro* by examining <sup>3</sup>H-thymidine uptake into DNA of rat breast carcinomas such as 7,12-dimethylbenz-(a)anthracene (DMBA)-induced breast carcinoma of rats, Shionogi mouse breast carcinoma type 115 and type 42, and human breast carcinomas. Tumor tissue was incubated with estradiol-17β or testosterone and with <sup>3</sup>H-thymidine-6-T. In DMBA-induced breast tumors, <sup>3</sup>H-thymidine uptake was markedly increased by addition of estradiol-17β and decreased by addition of testosterone. These tendencies were more exaggerated in tumor tissue from ovariectomized rats than in tissue from intact rats. In Shionogi carcinoma 115 (an androgen-dependent tumor) uptake of <sup>3</sup>H-thymidine was decreased by estradiol-17β and increased by testosterone; sensitivity to testosterone was more pronounced in tumor tissue from castrated mice than in tissue from intact mice. In Shionogi carcinoma 42 (a hormone-independent tumor), <sup>3</sup>H-thymidine uptake was not affected by either estradiol-17β or by testosterone. Of 39 human breast tumors, 18 were classified as estradiol-dependent, 12 as estradiol-independent, and 9 as "estradiol suppressive". Fifteen of the human tumors were from premenopausal women and 24 were from postmenopausal women. Seventy-three percent of tumors in the premenopausal group were estradiol-dependent while the tumors from postmenopausal women were evenly distributed into the estradiol-dependent, estradiol-independent and estradiol-suppressive groups. Two testosterone-dependent human tumors were found, both in postmenopausal women.

0839 METABOLISM OF RNA IN NORMAL AND LEUKEMIC CELLS. (E.) Cline, M. J. (U. California Sch. Med., San Francisco). *Acta Haemat* 45:174-180, 1971.

Various features of RNA metabolism in normal and malignant human leukocytes are discussed with emphasis on the rate of RNA synthesis and turnover in human leukocytes. In mammalian cells generally, the nucleus appears to be the major site of RNA synthesis while the nucleolus appears to be the primary site of ribosomal RNA synthesis. The principal species of RNA made by mammalian cells are a

low molecular wt 4S RNA (principally transfer RNA), a high molecular wt RNA, and messenger RNA. In addition, considerable quantities of 5S and several other species of RNA are synthesized; the function of these "minor" RNA components is not known. The basic features of RNA metabolism in mammalian cells also characterize RNA metabolism in human leukocytes. Leukemic blast cells have been shown to contain more RNA than differentiated end cells; lymphoblasts and myeloblasts also have very high rates of RNA synthesis and turnover. RNA synthesis in lymphoid cells can be influenced by exposure of cells to specific antigens or to nonspecific mitogens (e.g., phytohemagglutinin). Phagocytosis has been shown to modify RNA metabolism in differentiated granulocytes. The turnover rate of leukocyte messenger RNA is a function of the morphologic type of leukocyte; the turnover rate of RNA is faster in leukocytes than in bacterial cells but slower than in erythrocytes and hepatocytes. The highest recorded messenger RNA turnover rate in man was seen in a patient with macroglobulinemia and lymphosarcoma. Unanswered questions regarding leukocyte RNA metabolism include questions as to the function of 5S RNA, the metabolism of RNA in regard to cell differentiation, the role of RNA in the interaction between macrophage and antigens with sensitized lymphocytes, and the possibility of different patterns of RNA synthesis and control in normal and in malignant cells.

- 0840      NORMAL AND PHYTOHEMAGGLUTININ-TRANSFORMED HUMAN LYMPHOCYTES *IN VITRO*: MOLECULE CYTOLOGY AND PATTERNS OF  $^3\text{H}$ -THYMIDINE,  $^3\text{H}$ -URIDINE AND  $^3\text{H}$ -LEUCINE INCORPORATION. (Sp.) Bover, G. G. (Inst. Cytology Res., Valencia, Spain), R. B. Candela, A. M. Ramon. *Sangre* 16(2):185-232, 1971.

The dynamics of DNA, RNA and protein synthesis in phytohemagglutinin-transformed human lymphocytes, *in vitro*, were investigated by observations of  $^3\text{H}$ -thymidine ( $^3\text{H}$ -T),  $^3\text{H}$ -uridine ( $^3\text{H}$ -U) and  $^3\text{H}$ -leucine ( $^3\text{H}$ -Leu) incorporation. Autoradiography included also observation of silver granules over the  $^3\text{H}$ -T-labeled cell nuclei and over the  $^3\text{H}$ -U and  $^3\text{H}$ -Leu-labeled cell nuclei and cytoplasm. Heparinized peripheral blood was subjected to phytohemagglutinin treatment (0.25 ml/10 ml blood) for 3, 6, 12, 18, 24, 30, 36, 48, and 72 hr. Aliquots were then treated with  $^3\text{H}$ -T,  $^3\text{H}$ -U or  $^3\text{H}$ -Leu resp. 1 hr before the cell culture was subjected to autoradiography. DNA replication started 30 hr following phytohemagglutinin treatment, increased through 72 hr and then decreased. Three patterns of DNA synthesis were observed; one occurred as diffuse distribution of silver granules throughout the euchromatin with no involvement of perinucleolar or intranucleolar chromatin. This pattern coincided with the initial stage of  $^3\text{H}$ -T incorporation. Another pattern, occurring later, revealed the localization of silver granules over the heterochromatin; the third pattern revealed the exclusive accumulation of silver granules over the

perinucleolar or intranucleolar chromatin. RNA synthesis was observed 3 hr following phytohemagglutinin action, reaching a peak rate at 18 hr. An exponential accumulation of RNA in the granular portion of the nucleolus was observed through 72 hr after the initiation of cell culture. RNA appeared to be present in euchromatin but not in heterochromatin, indicating the occurrence of RNA synthesis independent of synthesis taking place within the nucleolus. Protein synthesis started 3 hr after the experiment began and increased in rate through 6 hr, maintaining this rate through 72 hr.  $^3\text{H}$ -Leu incorporation was more intense in the nucleolus than within the cytoplasm. The importance of the finding of intranucleolar protein synthesis in phytohemagglutinin-transformed cells is emphasized.

- 0841      LACK OF CORRELATION BETWEEN THE PRESENCE OF CIRCULATING TUMOR CELLS AND THE DEVELOPMENT OF PULMONARY METASTASES. (E.) Crile, G., Jr. (Cleveland Clin. Fdn., O.), W. Isbister and S. D. Deodhar. *Cancer* 28(3):655-656, 1971.

A sarcoma was implanted in the left hind legs of strain A/jax mice and the affected legs were amputated 14 days later. Blood from amputated mice was injected into the thighs of syngeneic mice; no tumors grew in thighs of these recipients. Lungs from tumor-bearing amputated mice were minced and lung tissue was injected into the thighs of syngeneic mice; all of 8 mice given injections of lung tissue developed thigh tumors. Evidently not enough tumor cells circulated in the blood to enable the tumor to be transferred by injection of blood, whereas there were enough tumor cells in the lungs to cause prompt growth of tumor in mice injected with lung tissue. In a related experiment, tumors implanted in feet of mice were left untreated until 7 days after implantation. On day 7, blood from tumor-bearing mice was injected into the thighs of recipients; all of 4 recipients of blood developed tumors by 14 days after injection. Minced lung tissue from mice which had borne implanted sarcomas for 10 days also transferred the tumor to 100% of recipients. Evidently, enough tumor cells were present in the blood and lungs between 7-14 days after tumor implantation to permit transfer of tumor by injecting recipients with either lung tissue or blood. Mice implanted with sarcoma and subsequently amputated developed lymph node metastases but no pulmonary metastases; this indicated that, although tumor cells reached the lungs, they did not grow there as metastases.

- 0842      CLINICAL CHARACTERISTICS OF THE GENETIC VARIETY OF CUTANEOUS MELANOMA IN MAN. (E.) Anderson, D. E. (U. Texas M. D. Anderson Hosp., Houston). *Cancer* 28(3):721-725, 1971.



Clinical aspects of familial cutaneous melanoma were compared with aspects of non-familial melanoma in a survey of 106 familial and 2,128 non-familial cases. The average age at first diagnosis of melanoma among males with familial melanoma was 44-yr-old; among females with a familial condition, the average age at diagnosis was 46-yr-old. The average ages at first diagnosis of melanoma among non-familial male and female cases were 50- and 48-yr-old, resp. It was thought that the younger average age at diagnosis of melanoma in familial as opposed to non-familial cases reflected earlier onset of the condition in the familial cases, rather than earlier detection of the condition in familial cases. Patients with familial melanoma showed a high frequency of multiple primary lesions; among 36 familial patients, 6 had 2 or more primary melanomas. The overall frequency of multiple primary lesions among familial cases was estimated to average 14%. The survival rate among familial patients was higher than among non-familial patients. At 12 months after diagnosis the proportions of familial and non-familial patients surviving were .87 and .66, resp. The genetic mechanism underlying the familial type of melanoma is apparently complex and may involve several autosomal gene loci, in addition to a cytoplasmic component transmitted by an affected or carrier female.

0843      AUTORADIOGRAPHIC STUDIES ON THE KINETICS OF NUCLEAR-CYTOPLASMIC TRANSFER OF RNA IN BLAST CELLS OF ACUTE LEUKAEMIA. (E.) Quaglino, D. (Inst. Med. Path., U. Modena, Italy), U. Torelli, G. Emilia, A. De Pasquale and C. Mauri. *Acta Haemat* 45:192-200, 1971.

Nuclear-cytoplasmic transfer of RNA in leukemic blast cells was compared to that in normal, phytohemagglutinin (PHA)-treated cells. Material included peripheral blood lymphocytes from 3 normal subjects, and blast cells from 9 cases of untreated acute leukemia (5 myeloblastic, 3 lymphoblastic and 2 myelo-monocytic). Cell samples were treated with uridine-5-T and with <sup>3</sup>H-thymidine and studied by autoradiography. Leukemic cells showed considerably lower total grain counts than normal PHA-stimulated cells. Leukemic cells showed in all cases a much lower uridine incorporation in cytoplasm than did normal cells. Even in acute leukemia cases in which nuclear grain counts were fairly high, the shift of label from nucleus to cytoplasm after 4 hr of incubation was much delayed compared to normal cells. In normal PHA-stimulated cells the percentage of cytoplasmic grains varied from 30-40% while in leukemic cells it was usually below 15%. Leukemic cells also showed a reduced concentration of label in cell nucleoli. Within a given leukemic cell population there was an extreme variability of nuclear/nucleolar labeling. There was a positive correlation between degree of uridine uptake and percentage of thymidine incorporation.

0844      TURNOVER OF HeLa RIBOSOMAL RNA: THE CHARACTERIZATION OF A CLASS OF RNA IN HeLa CYTO-

PLASM DERIVED FROM 28S RNA. (E.) Nair, C. N. (E. I. du Pont de Nemours & Co., Wilmington, Del.) and E. Knight, Jr. *J Cell Biol* 50:787-794, 1971.

Physical and chemical properties of a class of RNA of HeLa cell cytoplasm were reported; the RNA sedimented between the 18S and the 28S RNA in HeLa cell cytoplasm and had a relative S value of 22. This 22S RNA was thought to be a true cytoplasmic component, rather than an artifact of cell rupture or of the method of RNA preparation. The amount of 22S in HeLa cytoplasm was thought to be approximately 2-4% of the 28S. The 22S RNA content of HeLa polyribosomes and the 22S RNA content of structures sedimenting at 74S, 60S and 45S was determined in sucrose gradient sedimentation experiments. The 22S RNA was found in polyribosomes and at 74S and 60S, but not at 45S. 22S RNA had a base composition and methyl content similar to those of 28S RNA. 22S RNA was evidently not a direct product of transcription; rather it is probably a derivative of 28S RNA arising as a consequence of turnover of 28S ribosomal RNA. An RNA sedimenting at 22S was also found in L cells.

0845      MEDIUM DEPLETION AND CONTACT INHIBITION OF REPLICATION: ABSENCE OF A SPECIFIC INHIBITOR. (E.) Smets, L. A. (Biol. Div., Euratom C.C.R., Ispra, Italy). *Cell Tissue Kinetics* 4(3): 233-240, 1971.

Mouse, 3T3 and human cells were grown in cultures in which the growth medium was changed daily, and in cultures in which the medium was replaced by fresh material only once in 8 days; cell growth was observed to test the hypothesis that contact inhibition is mediated by a diffusible factor. Human cells grown in a medium which was changed daily grew linearly whereas human cells grown in the same medium for 8 days began to decline in number on day 6 after the initiation of cultures. Mouse cells grown in media which were changed daily reached a plateau of cell growth on day 4 due to contact inhibition. Cell loss started on day 6 in mouse cell cultures in which the medium was not changed in 8 days. In a related experiment, quasi-confluent cultures of human cells were changed every 48 hr with medium from cultures of human or mouse cell cultures. Medium formerly used by human cells supported growth in human cell cultures; however, no replication occurred in human cell cultures in which the medium was changed with medium used by mouse cells. When medium used by 3-day cultures of mouse cells was supplemented by fresh medium or dialyzed against serum-free medium it was found that addition of fresh serum had only a small beneficial effect on growth; dialysis, however rejuvenated the used medium. Unsupplemented, undialyzed mouse cell medium failed to promote growth of cells in mouse cultures. The addition of nutrients including glucose, glutamine, BME vitamins and BME amino acids to mouse cell cultures promoted cell growth. When growth properties of several mammalian cell lines were compared it was found that cells less sensitive

to contact inhibition of growth were the cells which utilized nutrients from the medium most efficiently. It was concluded that specific growth inhibitors are not responsible for contact inhibition of cell growth in culture; contact inhibition was thought to be associated with nutritive exhaustion of growth media.

- 0846      CALCIUM METABOLISM IN TUMORS ITS RELATIONSHIP WITH CHROMIUM COMPLEX ACCUMULATION: III. STUDIES ON THE NATURE OF THE ANIONS INVOLVED IN THE *IN VIVO* PRECIPITATION OF CALCIUM. (E.) Anghileri, L. J. (U. Colorado Med. Ctr., Denver) and E. S. Miller. *Oncology* 25(3):210-224, 1971.

The incorporation of  $^{14}\text{C}$ -labeled sodium bicarbonate, sodium citrate, sodium oxalate and glucose into tumor-bearing animal tissues was investigated; tumors included lymphatic leukemia, Ehrlich carcinoma, melanoma and lymphosarcoma. After injection of labeled anions, tumor-bearing animals were killed and tissue samples were taken; The  $^{14}\text{C}$  from bicarbonate accumulated in greater amounts in bone from tumor-bearing animals than in other tissues. Concentrations of  $^{14}\text{C}$  from bicarbonate were higher in tissues of the various tumors than in blood. The  $^{14}\text{C}$  from oxalate accumulated almost exclusively in bone; tumor-bearing animals with higher calcification (e.g., animals with lymphosarcoma and lymphatic leukemia) showed higher incorporation of  $^{14}\text{C}$  from oxalate. It was also found that animals with this higher calcification incorporated relatively small amounts of  $^{14}\text{C}$  from oxalate in bone. Incorporation of  $^{14}\text{C}$  from citrate was much higher in tumor tissue than in bone. Radioactivity incorporated from glucose was measured in soluble fractions of tissues from tumor-bearing animals; animals with hepatoma accumulated more  $^{14}\text{C}$  from glucose in the soluble fraction than animals with Ehrlich carcinoma and animals with Ehrlich carcinoma incorporated more glucose  $^{14}\text{C}$  than animals with lymphatic leukemia or lymphosarcoma. In the insoluble fractions this situation is reversed. It was concluded that while the anions bicarbonate, oxalate and citrate may be involved in *in vivo* calcium precipitation in tumor-bearing animals, they are not as important as glycolysis intermediates. Because of its low solubility and the direct relationship it has with other metabolic processes which normally were impaired in tumors,  $\alpha$ -ketoglutaric acid seemed to be the most probable calcium-precipitating compound.

- 0847      EVIDENCE FOR THE PRESENCE OF TUMOR PEPTIDES WITH CORTICOTROPIN-RELEASING-FACTOR-LIKE ACTIVITY IN THE ECTOPIC ACTH SYNDROME. (E.) Upton, G. V. (VA Hosp., West Haven, Conn.) and T. T. Amatruda, Jr. *New Eng J Med* 285(8):419-424, 1971.

Two peptides with corticotropin-releasing-factor-

like (CRF) activity were isolated at autopsy from an oat-cell carcinoma of a patient; 2 similar peptides were isolated from a pancreatic tumor of another patient. Both patients had confirmed ectopic ACTH syndrome. One tumor peptide from the oat cell carcinoma and one from the pancreatic tumor showed migratory rates similar to that of ACTH on electrophoresis; both these peptides were assayed for ACTH-like activity in hypophysectomized rats and both lacked any direct adrenal-stimulating activity. In addition to these 2 peptides, which had the approximate molecular size of ACTH, 2 other peptides were present in oat cell carcinoma and pancreatic tumor; these latter peptides had the migratory rate of B-melanocyte-stimulating hormone, and were smaller than vasopressin. These peptides were also devoid of activity when assayed in hypophysectomized rats for direct adrenal-stimulating activity. All 4 peptides were homogenous on high voltage electrophoresis performed at pH 6.5. CRF assays in rats treated with chlorpromazine-morphine-pentobarbital showed ACTH-releasing activity comparable to the ACTH-releasing ability of 20-40 mU pressor activity of standard lysine vasopressin; no antidiuretic-hormone activity was seen for any of the tumor peptides. Amino acid analyses of the tumor peptides confirmed that they were peptide in nature and that they differed in composition from ACTH.

- 0848      KARYOLOGICAL PATTERNS AND EXPRESSION OF MALIGNANCY IN SOME HOMOLOGOUS MOUSE SOMATIC HYBRID CELLS. (E.) Belehradsk, J., Jr. (Gustave-Roussy Inst., Villejuif, France) and G. Barski. *Int J Cancer* 8:1-9, 1971.

Malignant mouse strain C3H fibroblasts were crossed with non-malignant strain BALB/c mouse embryo cells and karyological studies were run on the hybrid cell line (designated HyEN) to determine whether there was any relationship between the karyological features and malignancy expression in hybrid cells. Six clones derived from the HyEN cells were also studied. Malignant C3H parent cells had a modal chromosome number of 47 and non-malignant parent cells had modal numbers of 74-75. Hybrid HyEN cells showed a wide dispersion of chromosome numbers from 69-121 (mode = 116); this observed hybrid mode was less than the "ideal" sum of the modes of the 2 parental lines (= 122). The presence of hybrid cells in HyEN culture could be assessed by analysis of the distribution of chromosome numbers. This showed a high proportion of cells in the high ploidy range (i.e., 100) which was not seen in pure cultures of parental cells. Only 16% of mitoses in HyEN cultures had chromosome numbers close to those of the non-malignant parent cell line. S.C. injection of HyEN cells into 5 young adult (C3H/He x BALB/c) F<sub>1</sub> mice resulted in 3 rapidly-growing tumors. Among the 6 established clones of HyEN cells, 5 were tumorigenic in mice; the 1 non-tumorigenic clone had a modal chromosome number of 112-118, similar to the modal numbers of 2 of the tumori-



genic clones. Three of the tumorigenic clones had modes of 80, 98 and 129 chromosomes. Secondary cell lines, developed *in vitro* from tumors produced with HyEN clones, showed a tendency towards chromosomal loss relative to the respective original *in vitro* clonal lines. A more pronounced tendency towards chromosomal loss was seen in early cultures of HyEN cell-induced tumor cells after passage *in vivo*. Tumorigenic hybrid HyEN cells showed a wide range of chromosomal variants, and no conclusion was possible concerning a definite relationship between chromosomal deletion and malignancy in the hybrid cells.

0849 REGULATION OF DEOXYRIBONUCLEOTIDE SYNTHESIS BY RIBONUCLEOTIDE REDUCTASE IN LEUKEMIC LEUKOCYTES. (E.) Fujioka, S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.). *Acta Haemat* 45:159-166, 1971.

The levels of specific ribonucleotide reductase and the regulation of this enzyme system in the course of viral leukemogenesis was examined in female Swiss mice inoculated i.p. with Friend murine leukemia virus. Ribonucleotide reductase was purified from spleens of mice killed 5 days postinoculation. The partially purified enzyme from murine leukemic spleen had a requirement for dithiothreitol. ATP was required in the reduction of CDP. Slight stimulation by magnesium ion was observed. In a comparison of different cytidine nucleotides as substrates, the highest reduction rate was obtained with CDP. GDP reduction was increased by the addition of dTTP to the reaction. On day 2 after inoculation with murine leukemia virus the specific activity of spleen ribonucleotide reductase had risen to over 3 times that of the control; over the next 3 days there was a sharp increase in the enzyme level to a peak specific activity of about 13 times higher than the average for normal spleen. Thereafter a gradual decline was seen. Ribonucleotide reductase was also present in acute and chronic myelocytic leukemia leukocytes from human patients. No ribonucleotide reductase activity was seen in normal or in chronic lymphocytic leukemia leukocytes. Coenzyme B<sub>12</sub> did not stimulate ribonucleotide reductase from megakaryoblastic bone marrow.

0850 PATHWAYS OF PURINE RIBONUCLEOTIDE CATABOLISM IN EHRLICH ASCITES TUMOR CELLS *IN VITRO*. (E.) Crabtree, G. W. C. (U. Alberta Cancer Res. Unit., Edmonton, Canada) and J. F. Henderson. *Canad J Biochem* 49(8):959-963, 1971.

The conversion of the purine bases adenine, hypoxanthine and guanine to ribonucleosides and other purine bases was systematically studied to determine the relative sensitivities of different purine ribonucleo-

side monophosphates to dephosphorylation, and to evaluate the relative importance of different routes of purine ribonucleoside formation. Ehrlich ascites tumor cells were incubated *in vitro* with 20, 50 or 100  $\mu$ M <sup>14</sup>C-labeled adenine and the total amounts of synthesized radioactive purine ribonucleotides and purine bases other than adenine were determined. Ehrlich cells treated with <sup>14</sup>C-adenine catabolized up to 21.2% of the amounts of radioactive acid-soluble nucleotides which were formed. Radioactive nucleotides were catabolized principally by dephosphorylation of inosinate, xanthylate, adenylylate and guanylate. Incubation of tumor cells with 20 or 50  $\mu$ M of <sup>14</sup>C-adenine resulted in a markedly reduced level of dephosphorylation of purine nucleotides compared to levels which were observed when tumor cells were incubated with 100  $\mu$ M of <sup>14</sup>C-adenine. When Ehrlich ascites cells were incubated with 20, 50 or 100  $\mu$ M of <sup>14</sup>C-labeled hypoxanthine, cells catabolized a much larger proportion of nucleotides (up to 183%). Nucleotides were catabolized principally by dephosphorylation of inosinate and xanthylate; guanylate was also catabolized.

0851 HYBRIDIZATION PROPERTIES OF DNA SEQUENCES DIRECTING THE SYNTHESIS OF MESSENGER RNA AND HETEROGENEOUS NUCLEAR RNA. (E.) Greenburg, J. R. (Inst. Cancer Res., Philadelphia, Pa.) and R. P. Perry. *J Cell Biol* 50:774-786, 1971.

The relationship between mouse L cell heterogeneous nuclear RNA (NRNA) and polyribosomal messenger RNA (mRNA) was investigated in hybridization experiments conducted under conditions in which hybridization of RNA transcribed from DNA sequences of all degrees of repetition would be expected to occur. A fraction of NRNA and mRNA was found transcribed from highly reiterated DNA sequences. Hybridization was performed in formamide solutions at DNA excess. Most hybridizing NRNA and mRNA reacted at D<sub>0</sub>t values expected for RNA transcribed from nonrepeated or rarely repeated genome fractions (D<sub>0</sub>t = DNA concentration x time). A fraction of both RNA's, however, hybridized at D<sub>0</sub>t values about 10,000 times lower, indicating that these RNA's were transcribed from highly redundant DNA sequences. About 1.7 times more NRNA than mRNA hybridized to highly repeated sequences. In studies of the thermal stability of hybrid RNA's, hybrids formed by rapidly reacting fractions of NRNA and mRNA melted over a narrow temperature range, with a midpoint about 11°C below that of native L cell DNA; this suggested that the 2 hybrids were composed of partially complementary sequences with 11% mismatching of bases. Little if any mismatching of bases was indicated for slowly reacting fractions of NRNA, which melted within 4-6°C of native DNA. Hybrids of slowly reacting mRNA had a high thermal stability similar to that observed for hybrids of the slowly reacting NRNA component. Hybrids of lower thermal stability were formed when relatively high inputs of mRNA were used; a comparable phenomenon was not observed for NRNA. It was suggested that there is less similarity among the relatively rare DNA sequences coding for NRNA than there is among the rare DNA sequences coding for mRNA.

- 0852 INITIATION AND ESTABLISHMENT OF LYMPHOID CELL LINES FROM THE BLOOD OF HEALTHY PERSONS. (E.) Chang, R. S. (Sch. Med., U. California, Davis), M.-W. Hsieh and W. Blankenship. *J Nat Cancer Inst* 47(2):469-476, 1971.

Leukocytes harvested from 89 specimens of peripheral blood from 67 healthy persons were cultured and the spontaneous establishment of cell lines from the leukocytes was observed. Of 796 cultures, 81 (10.2%) yielded cell lines. The proportion of cultures capable of yielding cell lines appeared to depend on the source of leukocytes. Cultures prepared from the blood of one donor sometimes yielded a larger number of cell lines than those from the blood of another donor. Even different samples taken from one donor at different times varied in capacity to initiate cell lines. No cell lines developed from blood of 8 newborns or 44 umbilical cord blood specimens. Many cell lines subjected to serial culture division every 3 or 4 days lost growth vitality. Some lines degenerated as early as the third, others as late as the 104th subculture; one cell line grew actively at the 143rd subculture. By adjustment of the interval between culture divisions to the rate of cell multiplication, the *in vitro* lifespan of 3 or 4 lines was prolonged by at least 50 serial divisions. Since only a small proportion of cultures prepared from the blood of some adult donors yielded cell lines, it was thought that the number of cells capable of initiating lines was very small, and that such cells were not found in all cultures. Many lines of leukocytes contained no detectable Epstein-Barr virus antigen.

- 0853 EVIDENCE OF SIALIC ACID-LECITHIN BINDING AT THE PLASMA MEMBRANE IN THE PRESENCE OF CATIONS. (E.) Deman, J. (Physical Biochem. Lab., State U., Ghent, Belgium), P. M. Van Vaerenbergh and P. Joos. *Europ J Cancer* 7:317-323, 1971.

Lecithin was spread on aqueous solutions containing a fixed concentration of *N*-acetylneuraminic acid (NANA) and varying concentrations of physiological cations including calcium, magnesium, potassium and sodium. The decrease in the surface tension of the resulting solution was measured. The lowering of surface tension implied some kind of binding between the lecithin film and sialic acid in which the physiological cations played a part. Since there was no interaction in the absence of the cations, it was suggested that they played the part of a bridge between the 2 organic molecules. The interaction between the lecithin monolayer and NANA was most pronounced with calcium and potassium; the interaction reached peak values at low concentrations of calcium and potassium. The results suggested that in tumor cells there is a modification of the cell membrane permeability to protein by binding sialic acid to phospholipids; a role for sialomucin modulation in the transport of proteins from the membrane to the extracellular region in tumor cells was also indicated.

- 0854 THE FATE OF CIRCULATING METHYLCHOLANTHRENE TUMOR CELLS IN MICE WITH TUMOR-SPECIFIC IMMUNITY. (E.) Wexler, H. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), P. E. Chretien and A. S. Ketcham. *Cancer* 28(3):641-646, 1971.

3-Methylcholanthrene (0.1 ml) was injected into the leg muscle of female C57BL/6N mice, and tumors designated MCA tumors developed; tumor cell suspensions were prepared from the MCA tumor and injected into the left hind leg muscle of 23 syngeneic mice. When MCA tumor-cell induced tumors had attained diameters of 1.0 cm. the affected leg was amputated. Following amputation of the primary tumor, mice were challenged with  $10^3$  MCA tumor cells i.m. in the remaining hind leg; mice which had not been previously inoculated with tumor cells also received i.m. injections of tumor cell suspensions. Amputated mice which had had MCA tumors demonstrated tumor-specific immunity to i.m. tumor cell challenge. Twenty of 20 previously untreated mice developed leg tumors following i.m. injection of tumor cells; by contrast, only 3 of 20 mice which had had MCA tumors amputated developed leg tumors after i.m. challenge with tumor cells. Animals which were protected against i.m. tumor cell challenge were not protected against i.v. challenge with MCA tumor cells. When mice which had had MCA tumor-bearing legs amputated were given i.v. injections of tumor cells in the tail vein, 20 of 20 mice developed lung tumors. When mice which had had MCA tumor-bearing legs amputated were given i.v. injections of 1 ml. of blood aspirated from the right heart of tumor-bearing mice, 17 of 20 mice developed lung tumors. These results appeared to indicate that the induction of tumor immunity, as demonstrated by the destruction of i.m. tumor cell inocula, may not be reflected in a similar destruction of tumor cells in the circulating blood.

- 0855 MITOCHONDRIAL DNA OF AVIAN LEUKAEMIC MYELOBLAST: ISOLATION AND ELECTRON-OPTICAL CHARACTERISATION. (E.) Korb, J. (Czechoslovak Acad. Sci., Prague). *Neoplasma* 18(4):337-348, 1971.

Myeloblasts were isolated from blood of leukemic chickens and mitochondria were extracted from the myeloblasts; mitochondria were purified on sucrose gradients and disrupted by osmotic shock, whereupon they released cytochrome c molecules of circular monomers and dimers of DNA. Of the DNA molecules seen in preparations of osmotically lysed mitochondria 90-94% were in monomeric form, appearing as circular molecules 5.1  $\mu$  long; dimers were found in 5-8% of osmotically disrupted cells and trimers and tetramers were exceptional. In CsCl gradients, the total DNA exhibited 3 bands, A, B and C. The band A represented some 65% of total DNA, the C band contained 30% DNA, the B band was represented as a minor component (5%). The band C contained 92% circular molecules of double stranded DNA and 2% circular dimers. Six percent of



this fraction was represented by molecules of linear DNA. The band B contained besides circular monomeric molecules (74%) also open circular dimeric molecules (16%) and catenated dimers (9%). Trimers and tetramers occurring mostly in this fraction were observed only exceptionally (up to 1%). Cyclic DNA molecules in monomeric form had a contour length of 4.71  $\mu$ , and cyclic dimeric DNA molecules had a contour length of 9.67  $\mu$ . Under the electron microscope, circular molecules of monomeric mitochondrial DNA from leukemic myeloblasts took the form of open rings and showed twisted shapes. Mitochondrial DNA had a different thermal profile from that of nuclear DNA.

0856 ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE AND CONTACT INHIBITION. (E.) Heidrick, M. L. (Coll. Med., U. Nebraska, Omaha) and W. L. Ryan. *Cancer Res* 31:1313-1315, 1971.

The intracellular concentrations of adenosine 3',5'-cyclic monophosphate (cAMP) and of phosphodiesterase were determined in 6 tumorigenic and 2 nontumorigenic cell cultures including strain L, HeLa, HEp-2, FL Amnion, Ehrlich ascites tumor, WI-38 and Fibro-5 (human). Considerable variation in cAMP occurred, apparently related to the age of the culture. Measurable quantities of cAMP were found only in older cultures. cAMP was measured each day for 6 days in a strain L culture. The amount of cAMP increased sharply on the 4th day of incubation, coinciding with the development of a stationary population and with confluency of the cell sheet. Phosphodiesterase also increased in a similar but less dramatic manner. There existed a parallelism between population-doubling time in the different cell cultures and the level of cAMP. The 2 nontumorigenic cell cultures had considerably higher levels of cAMP than the transformed, tumorigenic cultures. Contact inhibition, it was thought, may be mediated by adenylyl cyclase activation in cell membranes, with a subsequent rise in cellular cAMP.

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ALAVI, I.A.  
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ALLEN, P.T.  
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AMATRUDA, T.T., JR.  
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ANDERSON, A.C.  
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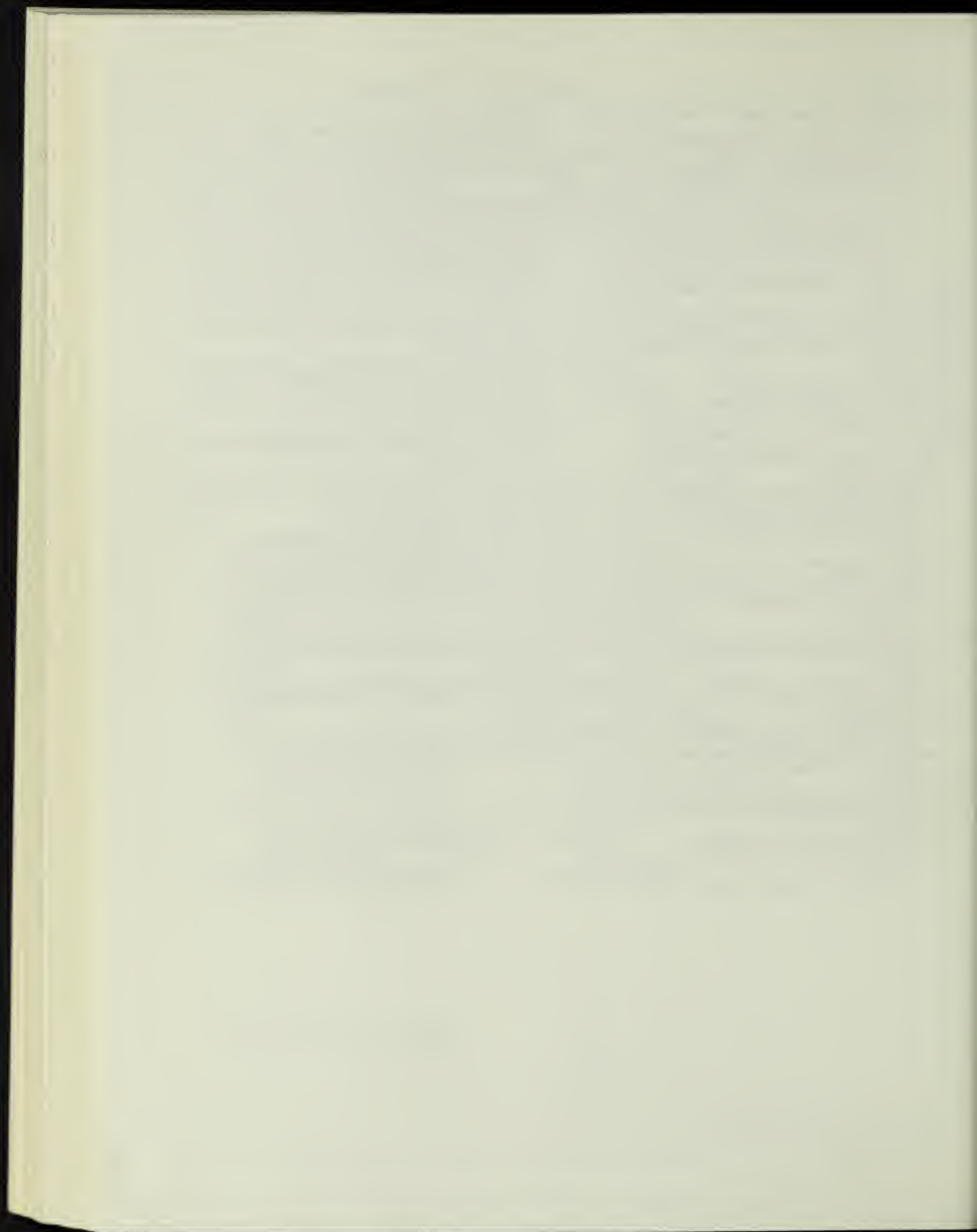
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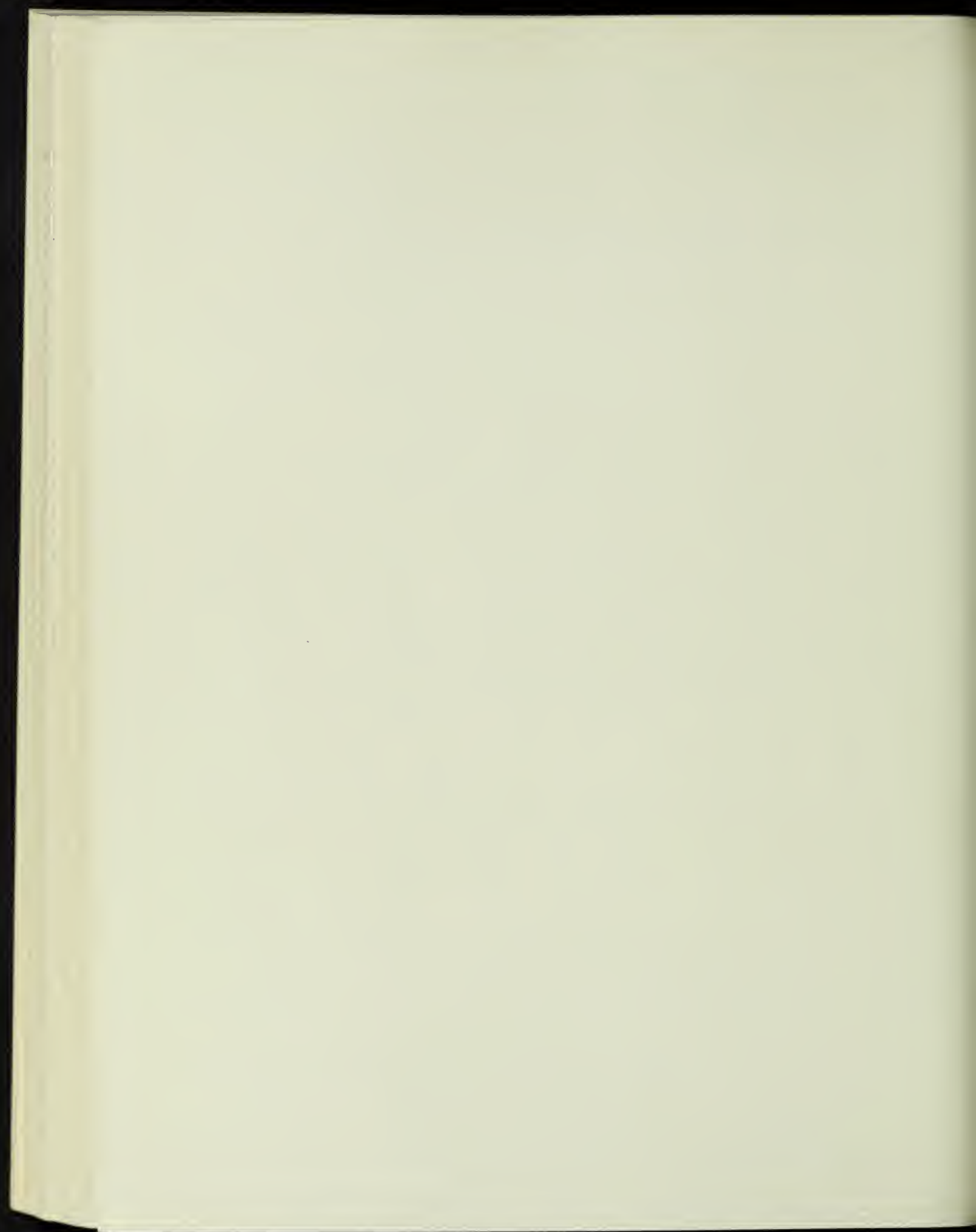
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# **CARCINOGENESIS ABSTRACTS**

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**Editor**

Robert Love, M.D.

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**Associate Editor**

George P. Studzinski, M.D.

Jefferson Medical College, Philadelphia

**NCI Staff Consultants**

Elizabeth Weisburger, Ph.D.

Sidney Siegel, Ph.D.

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## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain two-hundred abstracts and twenty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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## NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

### LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
ln.	Indonesian	Viet.	Vietnamese

### ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram ( $10^{-9}$ )
CNS	central nervous system	pg	picogram ( $10^{-12}$ )
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	U	unit(s)
kg	kilogram(s)	UV	ultraviolet
LD <sub>50</sub>	median lethal dose(s)	WBC	white blood cells (leukocytes), white blood count
m	meter(s)	wk	week
M	molar	wt	weight
mEq	milliequivalent(s)	yr	year(s)
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		





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## REVIEW

### ALPHA-FETOPROTEIN IN ONTOGENESIS AND ITS ASSOCIATION WITH MALIGNANT TUMORS. (E.)

v, G. I. (N. F. Gamaleya Inst., Moscow, U. S. S. R.). *Advance Cancer Res* 14:295-358, 1971.

Present state of knowledge of the control of alpha-fetoprotein (AFP) synthesis in oncogenesis, and possible reasons for the resumption of AFP synthesis in tumors, are reviewed. AFP is produced during embryonic period and secreted into the blood by cells of hepatic parenchyma. Although adult animals and humans do not possess detectable levels of AFP, synthesis is resumed during development of hepatocellular carcinomas or germinal tumors with elements of embryonic cancer. The physicochemical properties of AFP are detailed and methods for detecting it are described. The two preferred sites of AFP production in ontogenesis, liver and yolk sac, are discussed. AFP synthesis is also seen during regeneration of liver; this phenomenon is discussed as a model for studying AFP synthesis in general. The discussion of AFP synthesis in liver cell carcinoma includes four major topics: the problem of the localization of AFP synthesis in liver cancer; the change of AFP in the blood of liver cancer cases; agar-gel precipitation; quantitative aspects of AFP production by liver tumors; and the influence of biologic and pathogenic factors on AFP production in hepatomas. AFP synthesis in teratocarcinomas is also discussed. (167 references)

### IMMUNOLOGICAL ASPECTS OF MALIGNANT DISEASE.

(E.) Johnson, F. L. (Roy. Alexandra Hosp. Sydney, Sydney, Australia). *Med J Aust* 2(58):317-320, 1971.

Immunological aspects of human neuroblastoma are discussed in the context of a general review of the present state of knowledge of immune responses to tumors. Indirect clinical evidence that immunological factors are involved in human malignant disease generally is described. The phenomenon of spontaneous tumor regression, the regression of tumor metastases after treatment of the primary tumor, and the association of malignant disease with congenital immunological disorders are among the indications that immunological factors operate in human cancer. The discovery that experimental animal tumors possessed specific tumor antigens absent from normal cells (tumor-specific transplantation antigens) was discussed, as was the finding that the primary response to these antigens was mediated by circulating lymphocytes. It was noted that the human neuroblastoma undergoes spontaneous regression more frequently than any other malignant tumor. Small "in situ" neuroblastomas were found during post-mortem examination of young infants 40 times as frequently as would have been expected from the calculated rate of occurrence of overt neuroblastomas. The indication that host immunity may play a role in the regression of neuroblastomas gains support from the observation of lymphoid follicles and plasma cells in neuroblastoma sections. Experiments using Moloney sarcoma virus-induced sarcomas in mice as a model for human neuroblastoma indicated that there was a difference between animals in which the tumor regressed and those in which the tumor persisted; the two groups

were distinguished by the presence of a blocking antibody which was found only in the serum of animals in which the tumor persisted. Other experiments, with human neuroblastomas, indicated that these tumors possessed tumor-specific antigens towards which both lymphocyte-mediated and plasma-mediated immune reactions can be detected. (39 references)

### 0903 EPIDEMIOLOGY OF BURKITT'S LYMPHOMA. (E.)

Burkitt, D. P. (Med. Res. Council, London, England). *Proc Roy Soc Med* 64(9):909-910, 1971.

The evidence leading to the hypothesis that Burkitt's lymphoma is caused by a virus is reviewed, and the presently favored theory of the etiology of Burkitt's lymphoma is described. Studies initially indicated that regions where Burkitt's lymphoma was endemic were characterized by certain climatic conditions and that warmth and moisture were essential factors. This led to the belief that an insect vector was implicated in the genesis of Burkitt's lymphoma; this belief was substantiated by the similarity of geographical pattern of Burkitt's lymphoma and certain vector-transmitted diseases. The Epstein-Barr virus became the favored candidate for the insect-transmitted etiological agent in Burkitt's lymphoma. Later investigation indicated that the vectored virus theory of Burkitt's lymphoma etiology could not be substantiated; for it became clear, both that there were moist tropical areas where the condition did not occur, and that the condition did occur in non-tropical regions. However, epidemiological studies confirmed that there is a close relationship between the incidence of Burkitt's lymphoma and the occurrence of malaria. Also, the finding that Epstein-Barr virus was always associated with Burkitt's lymphoma was upheld. A causal hypothesis which is consistent with available evidence is that Epstein-Barr virus, or other virus(es), acting on normal lymphoid tissue, is usually non-pathogenic, the virus rarely giving rise to malignant lymphoid proliferation. The same virus, acting in lymphoid cells which have been subjected to intense chronic malarial or possibly other infection, would still usually be non-pathogenic, but might be more likely to result in malignant change than when acting on normal cells. (32 references)

### 0904 TRANSMISSION OF CANCER IN MAN: TENTATIVE GUIDELINES REFERRING TO THE POSSIBLE EFFECTS OF INOCULATION OF HOMOLOGOUS CANCER EXTRACTS IN MAN. (E.)

Gross, L. (VA Hosp., Bronx, N.Y.). *Cancer* 28(3):785-788, 1971.

The production of tumors in humans by inoculation with human cancer extracts or cell suspensions is discussed. Implantation of viable tumor cells prepared from a cancer patient into close family members may readily result in the establishment of a progressively growing tumor in the recipient host. A reported case of transfer of a melanoma from a woman to her mother is described. In most cases in which viable cancer cells from humans are inoculated in unrelated humans, the inoculated tumor cells will not grow; however, there is at least one case on record in which a tumor "took" when implanted in such circumstances. There are several cases on record in which cancer has been

transmitted subsequent to kidney transplantation; in these cases, tumor cells were apparently transferred with the kidney transplant. Tumor development in kidney transplant patients is apparently facilitated by administration to transplant recipients of immunosuppressive drugs. In several patients who developed disseminated cancers after kidney transplantation, local and distant metastases have regressed following discontinuation of immunosuppressive drugs. Cases have also been reported in which patients develop primary malignant lymphomas while undergoing immunosuppressive therapy to prevent rejection of kidney transplants. (31 references)

0905 ANIMALS IN CANCER RESEARCH WITH REFERENCE TO VIRAL DISEASES. (E.) Muhlbock, O. (Netherlands Cancer Inst., Amsterdam). *Rev Roum Inframicrobiol* 8(2):69-76, 1971.

The uses of laboratory animals in cancer research are reviewed. The genetic constitution of animals is of paramount importance in the experimental study of tumors. Experiments with inbred animal strains (strains produced by brother-sister mating) have shown that autochthonous tumor incidence differs in different strains. The most commonly used animal in research is the mouse. In mice, genetic factors control the degree of susceptibility of different strains to chemical carcinogens. It has been shown that susceptibility to the development of cancers is not a genetic characteristic of the entire organism, but is limited to specific tissues and organs. Only with inbred strains can the relative importance of hereditary and environmental influences in cancer development be evaluated. There are at present about 200 different inbred strains of mouse. Inbred strains of mouse, observed over long periods, do show changes; however, inbred strains remain uniform by comparison to independently derived strains. The incidence of spontaneous mammary tumors in a given inbred mouse strain is not constant. Although mice of a given strain are alike genetically, they do not all develop a certain kind of tumor. Animal species other than the mouse are also used in the investigation of particular tumors: rats are used in the study of liver tumors and Syrian hamsters in the study of estrogen-induced kidney tumors. Adequate information about tumors is only available in domesticated animals. The investigation of tumor development in primates is hampered by the fact that the incidence of autochthonous tumors in primates is extremely low. Many problems with respect to laboratory animals used in cancer research still need to be solved. (14 references)

0906 WILD-TYPE GROSS LEUKEMIA VIRUS AND HERITABLE AUTOIMMUNE DISEASE OF NEW ZEALAND MICE. (E.) Mellors, R. C. (Cornell U. Med. Coll., New York, N.Y.). *Amer J Clin Path* 56(3):270-278, 1971.

Evidence that a murine leukemia-like virus (Gross leukemia virus) is implicated in autoimmune disease of New Zealand mice is reviewed. These mice, strains NZB and (NZB x NZW)<sub>F1</sub>, are widely studied as a model of interrelated autoimmune diseases which also affect man, including idiopathic glomerulonephritis, systemic lupus erythematosus, autoimmune hemolytic

anemia and malignant lymphoma. That murine leukemia virus (MuLV) is involved in these conditions as they arise in NZB mice is suggested by the finding of enveloped C-type RNA virus-like particles and budding virus-like particles typical of MuLV in thymus, spleen and kidneys of NZB mice. In addition, MuLV group-specific antigen has been demonstrated in extracts of spleen, kidney and milk of NZB mice, and the G soluble antigen of the Gross system has been found in plasma of NZB mice. NZB mice break tolerance to the G antigens and produce G natural antibodies in later life; some NZB mice also produce natural antibody to Gross leukemia virus envelope antigen. The severity of glomerulonephritis of both NZB and (NZB x NZW)<sub>F1</sub> mice increases as G natural antibody is formed and as the G soluble antigen undergoes immune elimination from the circulation. (60 references)

0907 BURKITT'S LYMPHOMA: A REVIEW OF THE PATHOLOGY, IMMUNOLOGY AND POSSIBLE ETIOLOGIC FACTORS. (E.) Wright, D. H. (No affiliation). *Path Annual* 6:337-363, 1971.

Clinical, histologic and cytologic features of Burkitt's lymphoma are reviewed; immunological studies of the condition are described, and possible etiologic agents are discussed. Clinically, Burkitt's lymphoma shows a predilection for the jaws, central nervous system, endocrine glands, gonads and abdominal viscera. Lymph nodes and spleen are not affected as commonly as the foregoing organs. Histologically, Burkitt's lymphoma shows large foaming non-neoplastic histiocytes exhibiting the so-called "starry-sky" pattern. Characteristic cytological features include an intensely basophilic cytoplasm in lymphoid cells. Clinical evidence for host anti-tumor immunity in Burkitt's lymphoma patients includes the finding that many cases show long-term remission with small doses of chemotherapeutic agents. This suggests that chemotherapy may tip the balance in favor of the host and that immune factors may play a part in both the destruction of the tumor and the maintenance of remissions. It is reported that serum from patients with Burkitt's lymphoma have a growth-promoting effect on freshly isolated Burkitt's lymphoma cells, while serum from patients in remission have a growth-suppressive effect on cultured cell lines from Burkitt's lymphoma tissue. Transient remission of Burkitt's lymphoma has been reported following infusion of plasma from patients in remission. The hypothesis that Burkitt's lymphoma is caused by a transmissible agent is discussed. Possible etiologic agents for Burkitt's lymphoma are thought to include Epstein-Barr virus, reovirus 3 and malaria (*Plasmodium falciparum*). (59 references)

0908 TUMOR IMMUNITY IN MAN. (E.) Southam, C. M. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.). *Memorial Sloan-Kettering Cancer Cen Clin E* 1(2):40-48, 1971.

A review of evidence for tumor immunity in humans is presented; the emphasis is on tumor immunity as it concerns the clinical oncologist. Clinical observations occasionally reveal complete, transient or



regressions of cancer, or lack of progression for a considerable period of time. When no other explanation for such reversals in disease progression is forthcoming, an activation of immune defense mechanisms may be hypothesized. The frequent occurrence of preneoplastic lesions and *in situ* carcinoma (e.g., endometrial hyperplasia and stage 0 cervical cancer) to progress into invasive cancer also suggests that defensive "surveillance" mechanisms detect and eliminate neoplastically transformed cells. In studies of patients in all stages of cancer, the number of cancer cells in peripheral blood was much greater than the number of metastatic foci of cancer. These observations may suggest a form of host resistance to tumor cell implantation and growth. Clinical experiments in tumor biology, including cancer cell autotransplantation, skin tests, experimental immunotherapy, and immunosuppression studies, are discussed. Studies indicate that human cancer autotransplants "take" frequently. In one study, it is reported that transplantation of a million cells to cancer patients produces cancer nodules in 50% of patients, while autotransplantation of 10,000 cells produces cancer nodules. It is also reported that immunologically normal patients are much more resistant to immunologically impaired patients to implantation of their own tumor cells. Clinical trials of active immunotherapy using various tumor preparations and sources of putative tumor-specific antigens have been reported periodically. Results of clinical immunotherapy trials cannot be dismissed as negative, as they do not give substantial evidence for anti-tumor immune reactions in man. Observations of inadvertent immunosuppression in human patients--especially organ transplant patients--have shown that more cancers develop in patients on long-term immunosuppressive regimens than would be expected to develop in a normal population. *In vitro* studies suggesting that there are auto-immune reactions to cancer cells are briefly discussed. (35 references)

#### EXPRESSION OF ANIMAL VIRUS GENOMES (E.)

Baltimore, D. (Dept. Biol., Massachusetts Institute of Tech., Cambridge). *Bact Rev* 35(3):235-241, 1970.

behavior of viral systems and the implications of their existence are presented. The process which viruses must perform is that of mRNA synthesis. The viral genetic system is delineated in terms of six classes: viruses which have a double-stranded DNA genome can express and duplicate their genetic material by processes similar to those used by cells; viruses with genomes of other types have other systems for replication and transcription. A central element in the genetic systems of many viruses is a polymerase carried in the virion which carries out a transfer of information from one type of nucleic acid to another. Information regarding poliovirus, vesicular stomatitis virus, and RNA tumor viruses is brought up to date, and implications for cell biology are discussed. For the picornaviruses encode multiple protein species in a single polypeptide; the rhabdoviruses and myxoviruses carry many genes in a single RNA but synthesize separate, complementary RNA species; and

the RNA tumor viruses probably transfer their genetic information from RNA to DNA. (48 references)

#### 0910 HUMORAL REGULATORS IN THE DEVELOPMENT AND PROGRESSION OF LEUKEMIA. (E.) Metcalf, D. (Walter and Eliza Hall Inst., Melbourne, Australia). *Advances Cancer Res* 14:181-230, 1971.

A review of present knowledge of the role of hormones and humoral regulators in leukemogenesis addresses itself to the following questions: Do specific humoral regulators exist for the various types of hematopoietic cells? Do abnormalities in the levels of these regulators or in the responsiveness of target cells to these regulators occur either before leukemia develops or during the disease? Do abnormalities in regulator-target cell interaction ever cause leukemia development or substantially modify the progression of the disease? It has been suggested that many leukemias might be caused by prolonged disturbances in levels of humoral white cell regulators. It is known that in endocrine tumorigenesis disturbance in the level of normal regulators can lead to tumor development; analogies between endocrine tumorigenesis and leukemia are explored. Regulation of hematopoiesis by erythropoietin, colony-stimulating factor, thymic humoral factors, thrombopoietin, and chalone or antichalone, is described. The influence on leukemia development of nonspecific humoral regulators of hematopoiesis, including cortisone, sex hormone and growth hormones, is examined. The possibility that abnormalities exist in the levels of some of these regulators during the preleukemic period is discussed. The production of humoral factors by leukemic cells, and the responsiveness of leukemic cells to humoral regulators, are described. A commonly accepted view of the involvement of regulators in leukemogenesis places regulator control mechanisms in the same category as immune responses; regulators, on this view, are components of a safeguard system for eliminating or suppressing abnormal hematopoietic cells. (242 references)

#### 0911 CHEMICAL CARCINOGENESIS: MECHANISMS AND APPROACHES TO ITS CONTROL. (E.) Miller, J. A. (U. Wisconsin Med. Ctr., Madison) and E. C. Miller. *J Nat Cancer Inst* 47(3):V-XIV, 1971.

Recent research on the metabolic activation of chemical carcinogens, and theories bearing on possible mechanisms of action of chemical carcinogens, are reviewed. The data on chemical carcinogens do not support the thesis that any chemical given chronically at high dosages will induce cancer in some animals. While no common structure is evident among known chemical carcinogens, the reactive forms of all appear to be strong electrophiles. The reactions of these electrophiles in cells involve nucleophilic molecules containing electron-rich atoms. Most chemical carcinogens require conversion *in vitro* to the reactive state. Metabolic reactions leading to the active x:y state and other metabolic reactions leading to the deactivation of x:y and its precursors account for many tissue and species differences in carcinogenic activity among chemical agents. Chemical carcinogens and chemical mutagens have much in common in that electrophilic reactants are the active forms of most,

perhaps all, carcinogens, and of many, but not all, mutagens. In the theory of the mechanism of chemical carcinogenesis, epigenetic as well as genetic mechanisms must be considered. Three genetic mechanisms are discussed. The first genetic mechanism is somatic mutation in which the copying of a chemically changed DNA leads to alterations of the DNA nucleotide sequence; such alterations would be perpetuated, with permanent changes in growth control. A second genetic mechanism involves the fixation in DNA of alterations occurring in RNA; this mechanism is based on the phenomenon of reverse transcription. A third genetic mechanism involves alterations which decrease the fidelity of the copying of DNA. Of epigenetic mechanisms of action for chemical carcinogens, two are discussed. The first such mechanism involves nongenomic changes leading to quasi-permanent changes in the transcription of DNA (including integrated virus genomes and "oncogenes"). The second epigenetic mechanism involves nongenomic changes leading to the preferential proliferation of previously existing preneoplastic or neoplastic cells (e.g., carcinogen-induced changes in host immunological capacity or hormone balance might give proliferative advantages to neoplastic cells). (36 references)

0912 THE APPLICATION OF CYTOCHEMICAL METHODS TO THE STUDY OF ACUTE LEUKEMIA: A REVIEW. (E.) Schmalzl, F. (Dept. Intern. Med., U. Innsbruck, Austria) and H. Braunsteiner. *Acta Haemat* 45(4):209-217, 1971. (59 references)

0913 THE SPECTRUM OF INFECTIONS WITH EPSTEIN-BARR VIRUS: A HYPOTHESIS. (E.) Evans, A. S. (Yale U. Med. Sch., New Haven, Conn.). *J Infect Dis* 124(3):330-337, 1971. (64 references)

0914 TRANSPLANTATION AND CANCER. (E.) Fortner, J. G. (Memorial Hosp., New York, N.Y.). *Clin Bull* 1(3):102-106, 1971. (25 references)

0915 RADIATION INJURY WITH PARTICULAR REFERENCE TO THOROTRAST. (E.) Grampa, G. (No affiliation). *Path Annual* 6:147-169, 1971. (199 references)

0916 ASBESTOSIS AND ALLIED DISEASES: ASBESTOS, SOME NONRADIOLOGICAL ASPECTS. (E.) Lawther, P. J. (St. Bartholomew's Hosp. Med. Coll., London, England). *Proc Roy Soc Med* 64(8):833-834, 1971. (11 references)

0917 EPIDEMIOLOGICAL ASPECTS OF ORAL CANCER. (E.) Ferrell, R. L. (U. Nebraska Coll. Med., Omaha), W. S. Carter and C. T. Yarrington, Jr. *Eye Ear Nose Throat Monthly* 50(10):386-390, 1971. (56 references)

0918 CHEMICAL CARCINOGENESIS. (E.) Ryser, H. J.-P. (U. Maryland Med. Sch., Baltimore). *New Eng J Med* 285(13):721-734, 1971. (113 references)

0919 CHROMOSOMAL ANOMALIES OF MULTIPLE MYELOMA: PERSONAL OBSERVATIONS AND A REVIEW OF THE LITERATURE. (Fr.) Rochon, M. (No affiliation), M. Cadotte, H. M. Pretty and L. A. Long. *Un Med Canada* 100(9):1750-1754, 1971. (22 references)

0920 TOXICOLOGY OF CYCLAMATES. (Ger.) Zbinden, G. (Inst. Pathol., U. Zurich, Switzerland). *Bibl Nutr Dieta* 16:38-49, 1971. (29 references)

0921 ETIOLOGICAL ASPECTS OF CARCINOMA OF THE COLON. (E.) Beazley, R. M. (U. Maryland Sch. Med., Baltimore). *Maryland Med J* 20(9):49-51, 1971. (14 references)

0922 THE SURGICAL PATHOLOGY OF THE REPRODUCTIVE SYSTEM AND BREAST DURING ORAL CONTRACEPTIVE THERAPY. (E.) Fechner, R. E. (No affiliation). *Path Annual* 6:299-319, 1971. (142 references)

0923 COINCIDENCE OF CARCINOMA AND LEUCOSIS. (Ger.) Schott, G. (Reg. Hosp., Zwickau, Germany). *Z Aerztl Fortbild* 65(15):787-797, 1971. (29 references)

0924 CANCER OF THE CHILD. (Sp.) Silva Sosa, M. (Children's Hosp., Mexico City). *Bol Med Hosp Infant* 28(4):463-466, 1971. (22 references)

0925 PATHOGENESIS OF CANCER. (Sp.) Meneses Hoyos, J. (Mexico City). *Med Rev Mex* 51(1115):427-436, 1971. (100 references)

0926 HISTOGENESIS AND MORPHOGENESIS OF TUMORS. (Rus.) Golovin, E. I. (Leningrad, USSR). *Arkhl Pat* 33(6):3-13, 1971. (82 references)

0927 STILBOESTEROL AND CANCER. (E.) Anonymous. *Brit Med J* 3(5775):593-594, 1971. (8 references)

0928 ULTRASTRUCTURAL PATHOLOGY OF HUMAN RENAL CELL TUMORS. (E.) Tannenbaum, M. (No affiliation). *Path Annual* 6:249-277, 1971. (45 references)

0929 THE ENIGMA OF NASOPHARYNGEAL CANCER: A SELECTIVE REVIEW INCORPORATING LOCAL EXPERIENCE. (E.) Peters, L. J. (Queensland Radium Inst., Australia). *Aust Radiol* 15(2):123-130, 1971. (48 references)



930 ULTRASTRUCTURE OF THE HUMAN MAMMARY GLAND.  
(E.) Ozzello, L. (No affiliation). *Path  
annual* 6:1-59, 1971. (61 references)

931 HOST FACTORS IN HUMAN MALIGNANT MELANOMA.  
(E.) Lewis, M. G. (No affiliation). *Path  
annual* 6:171-195, 1971. (98 references)

0932 THE EFFECT OF INTERFERON ON LEUCOCYTE FUNC-  
TION AND EXPERIMENTAL LEUKEMIA. (E.)  
Miller, R. K. (Grad. Sch., Rutgers U., New Brunswick,  
N.J.). *Newark Beth Israel Med Center* 21(2):103-112,  
1971. (9 references)

- 0933 THE INDUCTION OF ATP ENERGIZED MITOCHONDRIAL VOLUME CHANGES BY CARCINOGENIC N-HYDROXY-N-ACETYL-AMINOFLUORENES WHEN COMBINED WITH SHOWDOMYCIN: A UNITARY HYPOTHESIS FOR CARCINOGENESIS. (E.) Hadler, H. I. (Dept. Chem., Southern Illinois U., Carbondale), B. G. Daniel and R. D. Pratt. *J Antibiot* 24(7):405-417, 1971.

N-hydroxy-N-acetyl-2-aminofluorene (N-OH-AAF), a carcinogenic metabolite of N-acetyl-2-aminofluorene (AAF), was added to rat mitochondrial protein with shodomyacin and the pH was altered to 7.4. This combination induced an ATP energized mitochondrial volume change. The phenomenon was inhibited by the antibiotic oligomycin and thus was related to oxidative phosphorylation. Enhancement of the phenomenon occurred with the graded increase in concentrations of N-OH-AAF and with the increase of pH to 7.8. Next, the thiol reagent gramicidin was tested. In all the responsive systems (that is, gramicidin alone, gramicidin plus N-OH-AAF plus showdomycin, and gramicidin plus showdomycin), the addition of potassium ions was a requirement or had an enhancing effect on the positive ATP energized mitochondrial volume change. The change in volume in both instances occurs because N-OH-AAF interacts with the cycle that meshes with the respiratory chain. Because of this interaction a strategically located mitochondrial thiol group becomes unable to conjugate with the normal electrophilic acceptor located in the cycle which meshes with the respiratory chain. The thiol group thus becomes exposed. Once it is exposed, the group can be conjugated with a thiol reagent. The volume change data did not indicate whether N-OH-AAF was an uncoupling agent, but the oxygen electrode study established N-OH-AAF as a respiratory inhibitor. From this data, the authors hypothesize the following mechanism: when the carcinogen AAF is fed to rats, it is hydroxylated at the endoplasmic reticulum and N-OH-AAF is generated. This secondary chemical leaves the endoplasmic reticulum and interacts with the mitochondria, exposing the strategically located pivotal mitochondrial thiol group. The mitochondrial membrane is altered because of this and it becomes possible for genetic material to leak from the injured organelle. This genetic material acts like exogenous oncogenic virus, eventually changing the genome of the cell.

- 0934 PROMOTION BY PHENOBARBITAL OF HEPATOCARCINOGENESIS INDUCED BY ACETYLAMINOFLUORENE IN RATS. (E.) Peraino, C. (Argonne Natl. Lab., Ill.), R. J. M. Fry and E. Staffeldt. *Argonne Nat Lab Div Biol Med Res Ann Report* 1970:51-52.

Studies are reported in which rats were fed a diet containing 0.02% AAF for 11-26 days; AAF diet was followed by a control diet or by feeding with a diet containing 0.05% phenobarbital. By 260 days of treatment, 54 of 412 rats fed AAF followed by normal diet had developed hepatomas, while 209 of 420

rats fed AAF followed by a phenobarbital diet had developed hepatomas. Related experiments, designed to observe the proliferative activity of liver cells in rats fed phenobarbital for 72 hr before they were killed, suggested that phenobarbital stimulated cellular proliferation in the liver. It was concluded that phenobarbital enhances the expression of the neoplastic lesion previously produced by the carcinogen.

- 0935 STUDIES ON DNA REPAIR IN HUMAN LYMPHOCYTES TREATED WITH PROXIMATE CARCINOGENS AND ALKYLATING AGENTS. (E.) Lieberman, M. W. (U. Pittsburgh Sch. Med., Pa.), R. N. Baney, R. E. Lee, S. Sell and E. Farber. *Cancer Res* 31:1297-1306, 1971.

The effects of two proximate carcinogens,  $\beta$ -propiolactone, and N-acetoxy-2-acetylaminofluorene, and three alkylating agents, nitrogen mustard, methyl methane sulfonate and ethyl methane sulfonate, on DNA repair in human lymphocytes was studied. In the presence of hydroxyurea, used to suppress DNA synthesis of S phase cells, lymphocyte cultures treated with the compounds incorporated from four to nine times as much thymidine as did the controls. Results showed that about 90% of the lymphocytes participated in this response in contrast to the control preparations in which no more than 0.1 to 0.2% of the cells showed labeling with thymidine. No stimulation was noted with the precarcinogens dimethylnitrosamine, 3'-methyl-4-dimethylaminoazobenzene, and 2-acetylaminofluorene or with iodoacetamide which alkylates protein but not DNA. Electron micrographs of cells 15 hr after treatment with nitrogen mustard or methyl methane sulfonate showed considerable evidence of cellular damage marked especially by separation of the inner and outer nuclear membranes. Very little if any damage was seen with N-acetylaminofluorene.

- 0936 BINDING OF CARCINOGENIC AROMATIC AMINE TO RAT LIVER NUCLEAR ACIDIC PROTEINS *IN VIVO*. (E.) Lotlikar, P. D. (Temple U. Sch. Med., Philadelphia, Pa.) and W. K. Paik. *Biochem J* 124(4):443-445, 1971.

Livers of adult male rats pretreated with N-hydroxy-[9- $^{14}$ C]-2-acetamido-fluorene were perfused with sodium chloride and fractionation of liver proteins was performed. When liver nuclear proteins were fractionated by the procedure of Paik and Kim, the specific radioactivity of the sulfuric acid-insoluble fraction was about four times that of the sulfuric acid-soluble fraction. The proportions of radioactivity in the acid-insoluble and acid-soluble fractions were about 60% and 40% respectively of the total nuclear radioactivity. Radioactivity associated with the nuclear fraction may possibly indicate a fluorene residue binding to nuclear proteins. In the present studies the fluorene residues were bound to nuclear acidic proteins much more than to histones. In view of these results and in view of the suggestion that acidic proteins may be involved in the regulation of gene



pression in mammalian cells, it appears that modification of these acidic proteins by arylation with morene residues might alter their regulatory properties of gene expression and function.

37 A T4-BACTERIOPHAGE REVERSION TEST FOR THE NATURALLY OCCURRING MUTAGEN PRESENT IN BRACKEN FERN (*Pteridium aquilinum*). (E.) Roberts, I. M. (Dept. Biochem., U. North Wales, Bangor), D. S. Shaw and W. C. Evans. *Biochem J* 124(2):13p-14p, 1971.

A rapid and sensitive test was devised for the identification of the active principle of bracken fern, which poisons cattle and shows carcinogenic activity in small animals. By using a T4 rII mutant bacteriophage, which will not lyse an *Escherichia coli* strain with a  $\lambda$  prophage, it was possible to make the mutant revert to the wild type. The revertant r<sup>+</sup> genotype was then detected in the presence of the original T4 mutant by using *E. coli* KB ( $\lambda$ ) as indicator. This reversion test was found to give a positive response with about 1 mg of the base-analogue-type mutagens and 0.1 mg of N-methyl-N'-nitro-N-nitrosoguanidine. The bracken mutagen, eluted from a single spot of a t.l.c. plate, was active at a concentration of 0.25 mg. The method was found to be useful in following the chemical fractionation of the active principle.

38 THE POSSIBLE HUMAN HAZARD OF THE NATURALLY OCCURRING BRACKEN CARCINOGEN. (E.) Evans, A. (Dept. Biochem., U. Coll. North Wales, Bangor), Widdop, R. S. Jones, G. D. Barber, H. Leach, D. L. Jones and R. Mainwaring-Burton. *Biochem J* 124(2):1p-29p, 1971.

The carcinogenic bracken fern (*Pteridium aquilinum*) is described and the potential human hazard is discussed. Bracken extracts have caused cancer in rats, mice, quail and guinea pigs. Target organs vary with the species but include stomach, small intestine, lung, colon, lung, urinary bladder and the reticuloendothelial system. A possible human hazard associated with the bracken fern might come through direct consumption of bracken, as in Japan. Exposure to the bracken carcinogen might also be mediated by milk and dairy products (produced from cattle foraging on bracken fern), meat, or water supply. Studies with mice have demonstrated maternal transfer of the bracken carcinogen to offspring via the placenta and/or milk. Studies are presently underway to test the carcinogenic action of milk from cows which are given a bracken supplement by feeding the milk to rats and mice. A young calf, fed such milk, has shown impaired bone marrow activity.

939 EFFECT OF ALLOXAN DIABETES ON HEPATIC CARCINOGENESIS AND CIRRHOSIS IN A x C RATS GIVEN 2-DIACETAMIDOFLUORENE. (E.) Reuber, M. D. (Natl. Cancer Inst., Bethesda, Md.). *Gann* 62(3):157-161, 1971.

The role of the anabolic hormone, insulin, in tumor induction in A x C or Wistar rats was studied. Intact and castrated male and female rats with alloxan diabetes were fed 0.025% 2-diacetamidofluorene. It

was found that development of hepatic lesions in intact or castrated females or castrated males was not affected by diabetes. However, intact male rats (without diabetes) given the carcinogen-containing diet developed hepatocellular carcinomas and cirrhosis in high incidence. Intact male rats with diabetes did not develop carcinomas or cirrhosis of the liver. Similar results have been reported for the carcinogen, 2-acetamidofluorene. Since the effect of hormones in hepatic carcinogenesis is related to anabolic activity and specifically to protein synthesis, it was suggested that the anticarcinogenic activity of diabetes may well be related to its effect on protein synthesis via lack of insulin, rather than to disturbances in glycogen or fatty acid metabolism.

0940 BLOOD VESSEL TUMORIGENESIS BY 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE (SYMMETRICAL): GROSS, LIGHT AND ELECTRON MICROSCOPIC DESCRIPTIONS. I. (E.) Toth, B. (U. Nebraska Coll. Med., Omaha) and R. B. Wilson. *Amer J Path* 64(3):585-600, 1971.

It is reported that attachment of the dimethyl group to hydrazine (i.e., 1,2-dimethylhydrazine dihydrochloride (symmetrical) (DMH)) produces vascular tumors in mice; it was known that hydrazine itself induces lung tumors in mice. Seven-wk-old Swiss albino mice were given a 0.001% solution of DMH in drinking water for the remainder of their lives; the average daily intake of DMH was 0.058 mg for female mice and 0.087 mg for males. DMH substantially reduced the survival of treated mice compared to untreated controls. In DMH-treated females, 49 mice (98%) developed blood vessel tumors compared to 3% of untreated control females; 46 males given DMH (92%) developed vascular tumors compared to 1% of control males. The occurrence of vascular tumors in order of decreasing frequency was as follows; muscle, pararenal, fat, liver, parametrial, and paraepididymal tissues. Under the light microscope, blood vessel tumors had the appearance of angiosarcomas. Lesions were composed of elongated, flattened, spindle or polygonal-shaped cells lining the vascular clefts. Under the electron microscope, vascular lesions were composed of elements often occurring in hemorrhages, i.e., fibrinous material, red blood cells, fibroblasts, histiocytes, lipid droplets, etc. The incidence of lung tumors rose from 12% in untreated control females to 44% in DMH-treated females, and from 10% in control males to 24% in DMH-treated males.

0941 COCARCINOGENESIS: THE INTERACTION OF CHEMICAL AND PHYSICAL AGENTS. (E.) Vogel, H. H., Jr. (U. Tennessee Coll. Med., Memphis) and R. Zaldivar. *Radiat Res* 47(3):644-659, 1971.

A study is presented in which the effects of the physical agent, fission neutrons and the chemical carcinogen, 2,7-FAA (N,N'-2,7-fluorenylenebisacetamide), upon young adult male rats were examined. The primary objective was to determine whether the combined use of the 2,7-FAA and a single sublethal irradiation with fission neutrons might be additive or potentiative in the production of neoplasm. A significant conclusion of this work was the production of liver cancers through synergistic action; 52% of the rats treated with both agents showed evidence of hepatic carcinomas

and only 21% of those treated with the chemical alone showed liver neoplasia. The induction of stomach cancer also corroborated the synergistic action of the two agents when combined. The latent period for the induction of liver cancers was found to be much shorter than that for gastric cancers. Neither additivity nor potentiation however was found in relation to intestinal neoplasia. Adrenal and mammary gland tumors were observed in the animals treated with neutrons alone. Survival time is discussed; the most deleterious effects were ascribed to the neutron irradiation followed by the prolonged chemical carcinogen injections.

0942 BIOCHEMICAL STUDIES OF DIETHYLSTILBESTROL-INDUCED KIDNEY TUMORS IN THE GOLDEN SYRIAN HAMSTER. (E.) Lacomba, T. (Fac. Med., Valencia, Spain) and M. Cabaldon. *Cancer Res* 31:1251-1256, 1971.

The influence of sex, species, castration in males, and DES (diethylstilbestrol) pellet implantation upon the formation of DESGA (diethylstilbestrol monoglucuronide) by hamster liver homogenates was studied by examining the relationship between the levels of glucuronyltransferase activity toward DES and the induction of renal tumors. Two DES derivatives were used: DESGA and DESDME (diethylstilbestrol dimethyl ether). DES, DESGA, and DESDME were administered chronically to male hamsters in order to compare their tumorigenic activity on the kidney. Activities of UDP (uridine diphosphate) glucuronate glucuronyltransferase toward DES in hamsters treated with DES, of  $\beta$ -glucuronidase ( $\beta$ -D-glucuronide glucuronohydrolase) toward DESGA in hamsters treated with DESGA, and of O-demethylase toward DESDME in hamsters treated with DESDME were determined in liver homogenates. It was found that chronic administration of DESGA did not produce renal tumors in the hamster after 15 months. DESDME produced renal tumors in 80% of the hamsters by the end of 12 months and DES produced tumors by ten months. In the presence of UDPGA, glucuronyltransferase activity in kidney homogenates was approximately five times higher in the hamster than in the rat. In the absence of added UDPGA (endogenous activity), the differences of activity were not statistically significant. Hamsters with estrogen-dependent renal tumors had the same hepatic glucuronyltransferase activity as controls. Hepatic  $\beta$ -glucuronidase activity toward DESGA was not induced by DESGA treatment lasting ten months. Hepatic O-demethylase activity was not induced by DESDME treatment lasting 10.5 months. The presence of the NADPH-generating system (glucose 6-phosphate, NADP, and glucose 6-phosphate dehydrogenase) was indispensable for the functioning of the reaction.

0943 EFFECT OF BENZENE ON RAT LIVER POLYRIBOSOMES. (E.) Tryfiates, G. P. (West Virginia U. Med. Ctr., Morgantown). *Biochem Pharmacol* 20:1669-1677, 1971.

The effect of benzene on the optical density sedimentation behavior of liver polyribosomes and on the incorporation of labeled uridine into polyribosomes was studied. Male rats were given i.p. injections of 0.520-5.630 ml benzene followed immediately

by the injection of the radioactive RNA precursor. The animals were then sacrificed. Optical density sedimentation patterns of treated rats showed breakdown of liver polysomes and appearance of abnormally high monomer-dimer ribosomal peaks. In addition, a new ribosomal peak located between the monomer-dimer region of the gradient also appeared. The distribution of tritiated uridine was qualitatively similar to that of controls; the amount of radioactivity incorporated in the presence of benzene was, however, diminished considerably. The protein synthetic capacity of disaggregated liver polyribosomes as measured by incorporation of L-[ $^3$ H]-phenylalanine *in vitro* was considerably impaired (>50%) but the poly-U-directed polymerization of L-[ $^3$ H]-phenylalanine was not affected. Protein synthesis tests with polyribosomes and pH 5.1 enzyme fractions from benzene-treated and untreated animals showed that treatment with benzene *in vivo* did not affect the pH 5.1 enzyme fraction. To gather information on the effect of benzene on the liver radioactive label pool, the RNA precursor 5-[ $^3$ H]-orotic acid was given i.p. to untreated and to benzene-treated rats. The amount of specific radioactivity incorporated into the polyribosomes of untreated animals was about 40% of that incorporated into total liver RNA; however, only 20% of total liver RNA radioactivity was incorporated into polyribosomes of benzene-treated rats. Benzene did not affect the liver radioactive pool.

0944 ACYLATION OF CARCINOGENIC HYDROXAMIC ACIDS BY CARBAMOYL PHOSPHATE TO FORM REACTIVE ESTERS. (E.) Lotlikar, P. D. (Temple U. Sch. Med., Philadelphia, Pa.) and L. Luha. *Biochem J* 124:69-74, 1971.

Results of acylation with carbamoyl phosphate of N-hydroxy-AAF (N-hydroxy-2-acetamidofluorene), 3-methylthio-AAF, and 2-amino-3-methylthiofluorene are reported. The acylating activities of carbamoyl phosphate are then compared with those of acetyl-CoA and acetyl phosphate. Interaction with methionine was used as an assay system for studying the acylation reactions. Incubation of N-hydroxy-AAF in the presence of carbamoyl phosphate in tris-HCl buffer, pH 7.5, gave appreciable amounts of methionine and guanosine reaction products. However, in the absence of carbamoyl phosphate, N-hydroxy-AAF showed very little activity with these two nucleophiles. The methionine reaction product was identified as 3-methylthio-AAF. Acetate, phosphate and sulfate esters of N-hydroxy-AAF also reacted with methionine to form this product. These results indicated that the reactive derivative was a carbamate ester of N-hydroxy-AAF. Since it is suggested that carbamoylation of N-hydroxy-AAF and other hydroxamic acids might occur in biological systems non-enzymatically, these carbamate esters of carcinogenic aromatic hydroxamic acids, if formed, would be reactive with tissue nucleophiles. It is suggested that carbamoylation of hydroxamic acids might be one of the activation steps in their carcinogenic process.



5 RESPONSIVENESS OF HYPERPLASTIC LESIONS AND HEPATOMAS TO PARTIAL HEPATECTOMY. (E.) Iwagawa, T. (Fac. Med., U. Tokyo, Japan). *Cann* 62: 224, 1971.

Count of mitotic indices of male Donryu rats fed 0.03% 2-fluorenylacetylamide (2-FAA) or 0.06% 3'-methyl-(dimethylamino)-azobenzene (3'-Me-DAB) was used to investigate the responsiveness of hyperplastic lesions of the liver and hepatomas to partial hepatectomy. It was found that the responsiveness of the nodules decreased gradually with the growing size, but it never became completely negative. Free hepatomas with high mitotic level and a hemangioma revealed slight or no change in the mitotic index after hepatectomy. In 3'-Me-DAB-fed rats the hypertrophic liver cells and areas of small focal hyperplasia were reactive to partial hepatectomy even during administration of the carcinogen. In 2-FAA-fed rats the original mature liver cells were quite inactive as long as the carcinogen was administered, but 6 to 24 weeks after discontinuation of the carcinogen their responsiveness returned to the same or even higher level than that of the areas of nodules of hyperplasia. Histologically the hepatomas were all trabecular. Although histological observations suggested a stronger toxicity for 3'-Me-DAB, the results showed that the toxicity of 2-FAA on liver cells was intense while deviation from cellular morphology was slight.

46 ALKYLATION OF NUCLEIC ACIDS OF RAT LIVER AND LUNG BY DEUTERATED N-NITROSODIETHYLAMINE IN VIVO. (E.) Ross, A. E. (U. Nebraska Med. Ctr., Omaha), L. Keefer and W. Lijinsky. *J Nat Cancer Inst* 47(4):789-795, 1971.

The mechanism of carcinogenesis by N-nitrosamines is thought to involve metabolic conversion of the nitrosamines to an alkylating species, which then alkylates some components of the cell, most probably DNA; neoplastic transformation of the cell is the ultimate result. A solution of diethylnitrosamine (DEN) containing both the tritium- and deuterium-labeled forms of DEN was prepared; the solution was administered by gavage to 12 male MRC rats which were sacrificed 16 to 24 hr later. Sections of liver, lung, kidney and small intestine were excised from each animal. The RNA and DNA were isolated from each organ and were radioassayed by paper chromatography and mass spectrometry. Chromatography results indicate that the nucleic acids from the liver and lung possess radioactivity associated with the purine bases guanine and adenine, and that the parent ion is most probably 7-ethylguanine; however, there seems to be little incorporation of radioactivity via normal metabolic pathways because diazoethane is not formed. The nucleic acids from the intestine, on the other hand, had all their radioactivity derived from normal metabolic pathways; no radioactive alkylated bases could be found. Methylating impurities, giving rise to 7-methylguanine and 7-methyl-d<sub>3</sub>-guanine, were found in the mass spectrometry tests. The action of DEN as a carcinogen

in a particular organ does not seem to depend solely on the alkylation of nucleic acids of that organ since the proportion of alkylated guanine residues appears to be the same in the lung and liver nucleic acids.

0947 EFFECT OF DL-TRYPTOPHAN ON TUMORIGENESIS IN THE URINARY BLADDER AND LIVER OF RATS TREATED WITH N-NITROSODIBUTYLAMINE. (E.) Okajima, E. (Nara Med. U., Japan), T. Hiramatsu, Y. Motomiya, K. Iriya, M. Ijuin and N. Ito. *Cann* 62(3):163-169, 1971.

Experiments are described in which fifteen rats given drinking water containing 0.05% N-nitrosodibutylamine (NDBA) with a basal diet developed tumors of the urinary bladder and esophagus; 33.3% developed liver tumors. Fifteen rats receiving water containing 0.05% NDBA and 1.4% DLT in their diet also developed tumors of the urinary bladder and esophagus, but not in the liver. Nine rats receiving normal drinking water and 1.4% DLT in their diet and nine control rats did not develop hyperplasia or neoplasia in any organ. The results show that DLT completely inhibited the development of liver tumors induced by NDBA, but did not affect the high incidence of urinary bladder tumors induced by NDBA. These results also suggest that DLT has an antagonistic effect on hepatocarcinogenesis of rats induced by NDBA, or a protective effect against the toxicity of this chemical in rats, but that its effect is positively correlated with NDBA induction of urinary bladder tumors.

0948 SQUAMOUS CELL CARCINOMA OF THE RAT ENDOMETRIUM PRODUCED BY INSERTION OF STRINGS COATED WITH PARAFFIN AND POLYMER. (E.) Baba, N. (Coll. Med., Ohio State U., Columbus) and E. von Haam. *J Nat Cancer Inst* 47(3):675-685, 1971.

In a study of tumor ultrastructure, string coated with paraffin and vinyl copolymer resin was inserted into the uterus of 16 virgin female NIH black rats. The 12 rats which survived surgery were killed at intervals of 12 months. After ten months five squamous cell carcinomas and two squamous dysplastic lesions of the endometrium were found. The incidence of malignant lesion was 41.6%. Gross observation showed all of the lesions to be associated with severe pyometra. Light and electron microscopic observations showed that, in the dysplastic stage, nuclear abnormalities were moderate, and keratinization of the superficial epithelial cells was incomplete, with many vacuoles in these cells. In the middle layer of the dysplastic squamous epithelium, lysosomes were markedly increased. The malignant cells had marked irregularity of the nuclei, enlarged nucleoli, and advanced keratinization in the superficial layers of epithelium. The ultrastructure of the cancer cells was quite similar to that of cells of the endometrial squamous cell carcinoma induced by carcinogenic polycyclic hydrocarbons. It was

indicated that NIH black rats have a definite predisposition to polymer carcinogenesis of the endometrium, since the same experiment in mice and rabbits failed to produce malignant neoplasms of the endometrium. It was not determined whether the carcinogenesis in the present work resulted from a high sensitivity of the NIH black rat to the induction of endometrial carcinoma by polymers, or from the presence of chemical carcinogens in the mixture used to coat the string.

- 0949 CARCINOMA OF THE COLON AND RECTUM OF RATS BY RECTAL INFUSION OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Narisawa, T. (Akita U. Sch. Med., Japan), T. Sato, M. Hayakawa, A. Sakuma and H. Nakano. *Cann* 62(3):231-234, 1971.

Female Donryu rats were given 0.5 ml of an 0.25% aqueous solution of N-methyl-N'-nitro-N-nitrosoguanidine by rectal infusion for 32 days. Seven of the nine rats which survived for more than 30 wk had one or more tumors in the colon and rectum. All the 25 tumors observed were of a protruded type; nine were pedunculated polyps, 13 were sessile polyps and three were polypoid tumors with ulceration at the center. No tumors were found in controls. The tumors were classified into six histological types showing epithelial atypism, invasion, and protrusion of the muscularis mucosae into the polyps. No lymph node metastasis was seen. All the tumors produced were similar to human colo-rectal tumors in both gross and histological findings. It was concluded that the carcinogenic compound interacted directly with mucosa of the large intestine; however, most of the carcinogen solution infused into the large intestine was evacuated from the anus soon after the experimental procedure.

- 0950 NEW THIO DERIVATIVES OF CARCINOGENIC ARYL-AMINES: 5. RING-SUBSTITUTED METHYLTHIO-4-ACETAMIDOSTILBENES. (E.) Fletcher, T. L. (U. Washington Sch. Med., Seattle), M. J. Namkung, H.-L. Pan and C.-A. Cole. *J Med Chem* 14(11):1113-1115, 1971.

The synthesis and characteristics of five of the ring methylthio-substituted derivatives of 4-acetamidostilbene (4AAS) was carried out in order to elucidate the products of the nonenzymatic reaction of 4-acetoxy-4-AAS with methionine. The 2- and 3-methylthio-4-nitrostilbene were made by condensing the appropriate methylthio-4-nitrotoluene with benzaldehyde. The intermediate aldol formed in the first of these was dehydrated in refluxing DMSO. The corresponding 2'- and 4'-methylthio isomers were made similarly, starting with p-nitrotoluene and o- and p-methylthio-benzaldehyde. The fifth of the isomers (the 3'-methylthio-4-nitrostilbene) was synthesized by a Meerwein arylation reaction between 3-methylthio-benzenediazonium chloride and p-nitrocinnamic acid. Comparison by gas-liquid and thin-layer chromatography and mass spectrometry of each of the five isomers with the products formed from the reaction of N-acetoxy-4-AAS and methionine, or isolated from the liver proteins of rats administered N(OH)-4-AAS, shows an

apparent identity of 3-methylthio-4-AAS with one of the *in vitro* and one of the *in vivo* products.

- 0951 WHOLE-BODY AUTORADIOGRAPHY OF  $^{14}\text{C}$  SODIUM CYCLAMATE IN PREGNANT AND FETAL RATS. (E.) Schechter, P. J. (Dept. Pharmacol., U. Chicago, Ill.) and L. J. Roth. *Toxic Appl Pharmacol* 21(1):130-133, 1971.

The relative distribution of  $^{14}\text{C}$ -sodium cyclamate in fetal and maternal tissues of the full-term pregnant rat was investigated immediately after injection and at a time point corresponding to the estimated biological half-life of the compound. Adult non-pregnant and 21-day pregnant Sprague-Dawley rats were injected i.v. with 100 mg/kg of uniformly labeled  $^{14}\text{C}$ -sodium cyclamate. The animals were sacrificed at five min and at seven hr after injection. Whole body autoradiograms from sagittal sections of each animal were prepared. It was found that five min after injection into 21-day pregnant rats the isotope was seen to be distributed relatively evenly throughout the maternal tissues. A similar distribution was observed in nonpregnant females at five min after injection. The fetuses contained little or no radioactivity at this time. At seven hr after i.v. injection most of the radioactivity had disappeared from maternal organs. The same distribution was seen in the nonpregnant female at this time point. In contrast to the mother, the fetuses retained a significant amount of radioactivity in all organs visible. It was suggested that a more intensive study of possible adverse effects of cyclamate on the embryo and fetus (with special emphasis on the urinary bladder) are needed.

- 0952 CADMIUM-INDUCED LEYDIG CELL TUMORS OF THE ALBINO RAT: ENZYME STUDIES. (Ger.) Knorre, D. (St. George Hosp., Leipzig, Germany). *Acta Histochem (Jena)* 11(Suppl.):111-116, 1971.

A single s.c. injection of 550  $\mu\text{g}$  cadmium chloride/100 body weight produces testicular necrosis in rats within 48 hr; necrosis develops as a result of cessation of enzyme activity in testes. Two wk after total necrosis of seminal ducts, remedial inflammation of testicular interstitial tissue set in, coupled with simultaneous resumption of activity by oxidative and hydrolytic enzymes. A month later, scars appear on the peripheral parts of the testes, and oxyreductase and hydrolase activity drops again. After 10-12 months, a proliferation of interstitial cells occurs and enzymatic activity increases. Beginning with the 355th day following injection, five of 30 surviving rats developed bilateral Leydig cell tumors without metastases. The tumor cells are characterized by strong lactate dehydrogenase and  $\text{NADH}_2$ -nitro-BT-reductase activity. Succinicdehydrogenase activity is weak as is the activity of unspecific esterase. Thus, in advanced stages, a cadmium-induced acute testicular necrosis leads to the development of interstitial cell tumors and to a predominantly anaerobic metabolism; the end product of glycolysis is mainly lactic acid. The weak activity of mitochondrial succinicdehydrogenase is the manifestation of poor differentiation by the proliferated interstitial cells.



HISTOCHEMICAL ANALYSIS OF HYPERPLASTIC LESIONS AND HEPATOMAS OF THE LIVER OF FED 2-FLUORENYLACETAMIDE. (E.) Kitagawa, (Fac. Med., U. Tokyo, Japan). *Gann* 62:207-1971.

on the histochemical and histological relations between hyperplastic lesions and hepatomas developed in the liver of male Donryu rats fed a 0.03% fluorenylacetamide (2-FAA) diet were obtained in order to make a more distinct characterization of the lesions and to give further evidence of the relations. There was a decrease of  $\alpha$ -glucuronidase, glucose-6-phosphatase, canalicular  $\alpha$ -glucosidase, acid and alkaline phosphatase and glycogen levels in areas of hyperplasia. Decreases in these activities were more marked in nodules of hyperplasia (hepatomas) than in areas of hyperplasia. Hepatomas showed abnormal staining patterns and variability of enzyme levels within lesions although histochemical findings were generally alike in hepatomas and areas of hyperplasia. Histochemical findings indicated that the two kinds of hyperplastic lesions and hepatomas must be classified in the same category since they are definitely and persistently deviated from normal cells.

4 TOXICITY AND BIOCHEMICAL AND FINE STRUCTURAL EFFECTS OF SYNTHETIC AFLATOXINS  $M_1$  AND  $B_1$  IN RAT LIVER. (E.) Pong, R. S. (Massachusetts Inst. Tech., Cambridge) and G. N. Wogan. *J. Cancer Inst* 47(3):585-592, 1971.

Various dosage levels of aflatoxin  $M_1$  and  $B_1$  were injected into male Fischer strain rats for 14 days. The activity of liver nuclear RNA metabolism showing inhibition of RNA polymerase was examined in a group of rats which were fasted for 24 hrs and dosed by gavage with each aflatoxin suspended in saline. It was found that natural  $B_1$  was lethal at doses of 1.0 mg/kg and higher. Synthetic  $B_1$  and  $M_1$  caused mortality at 1.5 mg/kg, but lower doses of the synthetic toxins caused only transient growth suppression and weight loss, which were reversed by the end of the study period. With respect to nuclear RNA metabolism, a 1.0 mg/kg dose of natural  $B_1$  blocked incorporation to about 70% within 0.5 hr and maximal suppression (92%) was evident after 12 hr. The nuclear RNA/DNA ratio followed a similar pattern of change, being substantially reduced within 0.5 hr and maximally suppressed by 12 hr. The synthetic toxins were found to be less potent. Similar results were obtained as regards loss of RNA from the nucleus; natural  $B_1$  reduced the RNA/DNA ratio more at a dose of 0.5 mg than the synthetic toxins did at doses of 1.0 mg/kg. It was concluded that both the natural and synthetic aflatoxin  $B_1$  inhibit the activities of RNA polymerases I and II. The fact that synthetic  $M_1$  and  $B_1$  cause comparable effects on RNA metabolism suggests that only one isomer in the

racemic mixture of the synthetic compounds may be active.

0955 EARLY APPEARANCE OF EMBRYONIC  $\alpha$ -GLOBULIN IN RAT SERUM DURING CARCINOGENESIS WITH 4-DIMETHYLAMINOAZOBENZENE. (E.) Watabe, H. (Sch. Med., Hokkaido U., Japan). *Cancer Res* 31:1192-1194, 1971.

Studies are described in which hepatic tumors were induced in male rats fed a diet containing 0.06% 4-dimethylaminoazobenzene. At one to three wk intervals after the onset of carcinogen feeding, blood from rats was analyzed for serum  $\alpha_f$ -globulin.  $\alpha_f$ -Globulin appeared in many rats at an early stage (i.e., after three to four wk of 4-dimethylaminoazobenzene feeding). At the sixth to seventh wk, 76% of the 41 rats in the two test groups were  $\alpha_f$ -globulin-positive. Later, the number of  $\alpha_f$ -globulin-positive rats decreased, and at the 11-12th wk all but one rat were  $\alpha_f$ -globulin-negative. After 13 wk,  $\alpha_f$ -globulin reappeared in 27 of 33 of those rats which survived 19 or more wks. Twenty-six of these 27 rats developed hepatoma. In seven of 33 rats no hepatoma developed; four of these rats were  $\alpha_f$ -globulin-negative. In 20 of 22 rats (90%) in which  $\alpha_f$ -globulin appeared early, hepatomas developed, but six rats developed hepatomas without early appearance of  $\alpha_f$ -globulin. In this early stage, the average serum level of  $\alpha_f$ -globulin was 2-4 mg/dl; however, in the hepatoma-developing stage,  $\alpha_f$ -globulin concentration increased and reached 60-100 mg/dl. This later concentration corresponded to the  $\alpha_f$ -globulin level in the serum of newborn rats.

0956 HYPERBASOPHILIC FOCI AS SITES OF NEOPLASTIC TRANSFORMATION IN HEPATIC PARENCHYMA. (E.) Daoust, R. (Montreal Cancer Inst., Quebec, Canada) and R. Calamai. *Cancer Res* 31:1290-1296, 1971

Studies are reported in which the occurrence of hyperbasophilic regions and tumors was examined in livers of rats fed either (a) hepatocarcinogens, (b) hepatotoxic but non-carcinogenic agents, or (c) basal control diet. Rats were fed the carcinogens 3'-methyl-4-dimethylaminoazobenzene, 4-dimethylaminoazobenzene, or diethylnitrosamine. Noncarcinogenic azo-dyes used were 2-methyl-4-dimethylaminoazobenzene, 4-aminoazobenzene and azobenzene. Nodules developing into hepatomas appeared in livers of rats given carcinogens. No significant histologic change was seen in livers of rats given noncarcinogenic azo-dyes. Areas of nodular parenchyma showing abnormally high RNA staining with basic dyes appeared after three mo. in rats fed 4-dimethylaminoazobenzene, and after two mo. in rats fed either of the other two carcinogens. No hyperbasophilic foci were seen in livers of rats fed noncarcinogenic azo-dyes or basal control diets. This finding suggested a close correlation between the occurrence of hyperbasophilic foci and tumor formation. After mild RNase treatment some foci with hyperbasophilic properties showed no other apparent alterations compared to surrounding tissues. Most

foci, however, showed one or more additional modifications, but could still be distinguished from tumors. Hyperbasophilic foci thus differed from both regenerating parenchyma from which they arose, and from tumors. Hyperbasophilic foci may be a transitional tissue, and probably represent sites of neoplastic transformation.

- 0957 THE EFFECT OF SIMULTANEOUS AND ALTERNATE FEEDING OF FURYLURAMIDE AND 4-DIMETHYLAMINOAZOBENZENE IN RATS. (E.) Miyaji, T. (Osaka U. Med. Sch., Japan). *Doioku J. Exp Med* 103(4):371-379, 1971.

Rats show enlargement and hypertrophy of liver cells when fed on a diet containing feryluramide. Hybrid male rats at 6 months were divided into three groups; one group was given 4-dimethylaminoazobenzene (DAB) alone; another was given feryluramide alone; and a third group was given DAB and feryluramide simultaneously at various intervals. Treated rats were killed and the livers were excised and histologically fixed. Results indicate that simultaneous DAB and feryluramide feeding has a suppressive effect on hepatic carcinogenesis. Further, a lower concentration of protein-bound azodye was found in the liver, indicating that DAB was inhibited in some way in its action with liver molecules. Alternate feeding of feryluramide and DAB produced no macroscopic difference in the livers of rats fed DAB followed either by feryluramide or by a basal diet. Under these conditions feryluramide did not have any effect in promoting carcinogenesis or in inhibiting it. Since only simultaneous feedings of DAB and feryluramide could suppress development of carcinoma, it can be concluded that feryluramide either enhances DAB metabolism, or delays synthesis of protein to be bound by DAB, or competes actively with DAB for special proteins.

- 0958 LIVER AND LUNG TUMORS IN MICE EXPOSED AT BIRTH TO 4-DIMETHYLAMINOAZOBENZENE OR ITS 2-METHYL OR 3'-METHYL DERIVATIVES. (E.) Roe, F. J. C. (Chester Beatty Res. Inst., London, England), G. P. Warwick, R. L. Carter, R. Peto, W. C. J. Ross, B. C. V. Mitchley and N. A. Barron. *J Nat Cancer Inst* 47(3):593-601, 1971.

The response of mice to 4-dimethylaminoazobenzene (DAB) and its 2-methyl and 3'-methyl derivatives (2-methyl-DAB) and (3'-methyl-DAB), given on each of the first five days of life to pathogen-free Swiss mice is reported. The results clearly showed that all three test substances increased the incidence of liver cell tumors in male mice and that DAB was significantly more effective in this respect than either 2-methyl-DAB or 3'-methyl-DAB. None of these treatments increased the incidence of liver cell tumors in female mice. In contrast, the incidence of lung tumors was significantly raised by the

exposure to 2-methyl-DAB (females only) or 3'-methyl-DAB (both males and females), whereas treatment with DAB was without effect. In the present work the test substances were injected subcutaneously, so that they or their metabolites passed through the lungs before they reached the liver. A greater ability to react with lung tissue could explain both the higher lung tumor incidence and the lower liver tumor incidence in the groups treated with 2-methyl-DAB or 3'-methyl-DAB as compared with the group treated with DAB.

- 0959 SOME BIOCHEMICAL CHANGES PRECEDING REGRESSION OF 7,12-DIMETHYLBENZ(a)ANTHRACENE-INDUCED MAMMARY TUMORS FOLLOWING OOPHORECTOMY. (E.) Hilf, R. (U. Rochester Sch. Med. Dent., N.Y.), J. W. Battaglini, J. A. Delmez, N. Cohen and W. D. Rector. *Cancer Res* 31:1195-1200, 1971.

Growth of most 7,12-dimethylbenz(a)anthracene (DMBA)-induced adenocarcinomas is significantly inhibited after the removal of the ovaries of the tumor-bearing host. In order to determine some of the chemical changes preceding this type of tumor regression, adult female rats were given DMBA dissolved in sesame oil through a stomach catheter. The rats were palpated weekly for tumors, and eight to ten weeks after initiation of the carcinogen regimen, rats with one to five tumors were given carbon-14-labeled leucine and thymidine. One half hour later, these rats were oophorectomized. Results indicated that oophorectomy had no effect on the weight of the tumor within the first five days after surgery; however, the weight of the uterus did decrease by the fourth and fifth days. Enzyme activities, on the other hand, showed marked changes. Lactate dehydrogenase and phosphoglucose mutase activities were decreased at four days post-oophorectomy, while pyruvate kinase and glucose-6-phosphate dehydrogenase were decreased at five days. Slight but significant increases in the activities of aspartate aminotransferase and hexokinase were seen on days 1-4 post-oophorectomy. Isocitrate dehydrogenase, malate dehydrogenase, and  $\alpha$ -glycerolphosphate dehydrogenase were not affected. Relative to these enzyme findings, it was noted that the incorporation of uridine into RNA and leucine into protein was significantly decreased in the neoplasms by the fourth and fifth days. In conclusion, it is indicated that removal of endogenous estrogens leads to several significant biochemical alterations in carcinogen-induced mammary tumors and that DMBA-induced neoplasms may be more dependent on ovarian function than the uterus.

- 0960 ISOZYME PATTERN OF NON-SPECIFIC ESTERASE DURING CARCINOGENESIS. (E.) Yoshimura, Y. (Osaka U. Dental Sch., Japan). *Gann* 62:187-197, 1971.

Dedifferentiation patterns of non-specific esterase during carcinogenesis of the skin of mice and detection of esterase related to keratinization in epidermoid carcinoma of submaxillary salivary glands of male ddO strain mice are reported. Tumor induction was by use of DMBA (7,12-dimethylbenz(a)-anthracene). Enzyme assays, protein determinations and cell fractionation for subcellular components



re carried out on minced and homogenized normal tumor materials of the skin. Thin-layer acrylamide gel electrophoresis was used for nogramic determinations. It was found that esterase-Ia was the main esterase in the skin from birth to the third day. During tumorigenesis nogram patterns of well-keratinized carcinoma showed marked increase of esterase-I with simultaneous increase of esterase-II and esterase-III. Based on histological features of characterization, epithelial tumors in the submaxillary salivary gland presented a specific pattern of keratinization. The non-keratinizing type of submaxillary salivary gland tumors showed a high level of active form of esterase-Ia which was resistant to eserine and isopropyl fluorophosphonate, while the keratinizing type exhibited an active pattern of esterase-Ia and esterase-Ib, like carcinomas of the skin. Esterase-Ib was sensitive to both inhibitors.

61 CARCINOGENIC AND ADRENOCORTICOLYTIC DERIVATIVES OF BENZ[*a*]ANTHRACENE. (E.) Pataki, (Ben May Lab. Cancer Res., U. Chicago, Ill.), C. Guid, P. W. Rabideau, H. Huisman and R. G. Harvey. *Med Chem* 14(10):940-945, 1971.

Investigations of the relationship between the structure and the carcinogenic and adrenocorticolytic activity of a series of dimethyl, trimethyl, hydroxymethyl, and formyl derivatives of benz(a)anthracene are reported. Tests of the sarcomagenic activities of these compounds were conducted on male 25-day-old Long Evans rats by i.m. injection of 2.5 mg of compound dissolved in 0.5 ml of sesame oil. The experiment was terminated at nine months. Methyl substitution outside the critical region in the 1,2,3,4, and 5 positions was shown effectively to abolish sarcomagenic activity, whereas introduction of methyl groups into the 6,7,8, or 12 positions of these same hydrocarbons was without effect on biological activity.

62 TRANSPLACENTAL CARCINOGENIC EFFECT OF 3-METHYLCHOLANTHRENE IN MICE AND ITS QUANTIFICATION IN FETAL TISSUES. (E.) Tomatis, L. (Int'l. Agency Res. Cancer, Lyon, France), V. Turusov, D. Gibbert, B. Duperray, C. Malaveille and H. Pacheco. *Nat Cancer Inst* 47(3):645-651, 1971.

Study of the effect of the administration of 3-methylcholanthrene (MCA) to pregnant mice on their offspring is reported. Progeny of treated mothers were nursed either by their own mothers or by untreated foster mothers. The concentration of MCA in fetal tissues of offspring of MCA-treated mothers was also analyzed. Pregnant female CF-1 mice were given three intragastric doses of 2.8 mg MCA spaced within 24 hr. For analysis of the concentrations of MCA in fetal tissues, pregnant mice were given either three doses or one dose of 3.3 mg MCA. All pregnant mice treated with MCA and all except one of their offspring developed one or more tumors. A high incidence of tumors was found in offspring nursed by their MCA-treated mothers, as well as in mice nursed by untreated foster mothers. A slightly higher incidence of tumors, mainly lymphomas, was seen in mice born from treated

mothers and foster-nursed by untreated females than was seen in mice nursed by their own treated mothers. The interval, ranging from one to seven days, between administration of MCA and delivery, did not affect the incidence of tumor-bearing litters. In fetal mice whose mothers were given MCA, the differences between total radioactivity and activity attributed to MCA alone indicated that only about 0.9% of total radioactivity could be attributed to unchanged MCA.

0963 EFFECT OF 3-METHYLCHOLANTHRENE ON GLUCURONYL TRANSFERASE IN HEPATIC MICROSOMAL SUBFRACTIONS. (E.) Howland, R. D. (U. California, San Francisco) and A. Burkhalter. *Proc West Pharmacol Soc* 13:8-12, 1970.

Guinea pigs and rats were treated with 3-methylcholanthrene i.p. in amounts of 40 mg/kg. In untreated adult guinea pigs, the ratio of glucuronyl transferase in the rough-surfaced microsomal liver fraction (RSM) to that in the smooth-surfaced microsomal liver fraction (SSM) was 2:1 for both *o*-aminophenol and *p*-nitrophenol conjugation. 3-Methylcholanthrene did not affect the conjugation of either substrate in guinea pig liver. The distribution of microsomal protein between SSM and RSM subfractions was approximately equal, and 3-methylcholanthrene did not alter it. In contrast to the guinea pig, the ratio of glucuronyl transferase-specific activity in the weanling rat RSM subfraction to that in the weanling rat SSM subfraction was about 1:1 in both treated and untreated animals, and for both *o*-aminophenol and *p*-nitrophenol substrates. 3-Methylcholanthrene pretreatment resulted in a 2-fold increase in enzyme activity for *o*-aminophenol and *p*-nitrophenol conjugation in all fractions. Unlike the guinea pig, distribution of protein between subfractions of weanling rat liver was not equal. Control untreated rats had nearly three times as much protein in RSM as in the SSM subfraction. 3-Methylcholanthrene significantly decreased the amount of protein in SSM and significantly increased the amount of protein in RSM. An increase in the RSM:SSM activities of *o*-aminophenol conjugation in adult rats as compared to weanling rats, with no corresponding alteration in *p*-nitrophenol conjugation, supported the hypothesis that there is more than one glucuronide transferase.

0964 TOXICITY OF AROMATIC HYDROCARBONS ON NORMAL HUMAN EPIDERMAL CELLS *IN VITRO*. (E.) Dietz, M. H. (Temple U. Hlth. Sci. Ctr., Philadelphia, Pa.) and B. A. Flaxman. *Cancer Res* 31:1206-1209, 1971.

Fragments of normal human abdominal skin were cultured in clots of chick embryo extract and plasma. The growth medium was replaced after ten days in culture with medium containing MCA or BP. Cultures



were maintained for three mo. after exposure to carcinogens. After four days of exposure to carcinogens, ten of 13 MCA-treated cultures, and all of 14 BP-treated cultures, showed a striking reduction in the amount of epithelial outgrowth when compared with control cultures. The effect was more pronounced in BP-treated than in MCA-treated cultures. No cells with enhanced growth properties were seen, and there was no evidence of malignant transformation. Within one wk after exposure to carcinogen, the well-ordered arrangement of cells seen before treatment and in untreated cultures diminished, and intercellular relationships became increasingly disordered and giant cells appeared. Giant cells also appeared in untreated cultures, but only after 10-12 wk.

0965 CELLULAR INJURY AND CARCINOGENESIS: THE EFFECT OF A PROTEIN-FREE HIGH-CARBOHYDRATE DIET ON THE METABOLISM OF DIMETHYLNITROSAMINE IN THE RAT. (E.) Swann, P. F. (Middlesex Hosp. Med. Sch., London, England) and A. E. M. McLean. *Biochem J* 124(2):283-288, 1971.

Porton-Wistar-derived albino rats and Sprague-Dawley rats were divided into two groups; one group was fed commercial pelleted diet, while the other group received a protein-free diet consisting of 65% corn-starch, 30% sucrose, and 5% olive oil. After seven days, the effect of a protein-free diet on the rate of metabolism of dimethylnitrosamine was assessed by measuring the rate of disappearance of dimethylnitrosamine from the blood of the animals. By linear regression analysis, it was determined that it took nearly eight hr longer to rid the blood of dimethylnitrosamine in rats fed on a protein-free diet than in rats fed the commercial diet. Next, dimethylnitrosamine was radioactively labeled and introduced onto pieces of lung and kidney tissue from the two groups of rats. It was found that rat livers subjected to a normal diet metabolized twice the amount of chemical compared to rat livers from the protein-free group; but the rate of kidney metabolism was the same for both. However, when dimethylnitrosamine is metabolized, it reacts with component sites of guanine to form a methylation product. Taking this into consideration, methylation of kidney nucleotides was found to be more than three times as great in the rats fed on a protein-free diet as in those rats fed on a normal diet. Data derived from mathematical evaluation of *in vivo* and *in vitro* studies confirm these results. This work also demonstrates the intimate relationship between diet and the carcinogenic and toxic effects of dimethylnitrosamine, since all of the animals on a protein-free diet developed tumors (resembling Wilms tumors) after chemical injection.

0966 METHYLATION OF NUCLEAR PROTEINS BY DIMETHYLNITROSAMINE AND BY METHIONINE IN THE RAT *IN VIVO*. (E.) Turberville, C. (Med. Res. Coun. Labs., Carshalton, England) and V. M. Craddock. *Biochem J* 124(4):725-739, 1971.

Experiments investigating histone methylation by various compounds are described. Labeled compounds in-

jected into rats were methionine and dimethylnitrosamine. Liver and kidney histones were isolated and hydrolysates were analyzed by column chromatography. Enzymatic methylation was identified and separated from chemical methylation. Data suggested the possibility that methionine residues in histones were alkylated to give methylmethionine residues. Liver histones were about four times as alkylated as kidney histones. Possible role of the effects of alkylation on histone function in regard to carcinogenic alkylation was considered.

0967 THE INHIBITION OF DIMETHYLNITROSAMINE CARCINOGENESIS IN RAT LIVER BY AMINOACETONITRILE. (E.) Hadjiolov, D. (Oncol. Res. Inst., Sofia, Bulgaria). *Z Krebsforsch* 76(2):91-92, 1971.

Studies performed to determine the effect of aminoacetonitrile (AAN) on dimethylnitrosamine (DMN) carcinogenesis in rats are reported; AAN inhibits the metabolism of DMN. Male rats were divided into two main treatment groups: group 1 was given 1 mg DMN/rat/day in drinking water; group 2 was given the same DMN dose together with 20 mg AAN injected three times/wk. Animals in group 1 died within 20-24 wk. Seven of ten rats in this group had liver hemangioendothelial sarcomas, hepatocellular carcinoma, and hepatoma. No liver tumors were discovered in rats of group 2; however, leukemic infiltration of the liver was present in two of 11 of these rats.

0968 INFLUENCE OF METHYLNITROSOUREA ON MALIGNANT TRANSFORMATION OF MOUSE EMBRYO CELLS IN TISSUE CULTURE. (E.) Frei, J. V. (Dept. Path., U. Western Ontario, London, Canada) and J. Oliver. *J Nat Cancer Inst* 47(4):857-863, 1971.

An investigation of the ability of methylnitrosourea (MNUA) to influence the transformation of mouse embryo cells is reported. CFW/D inbred Swiss mouse embryo cells were treated with MNUA at a concentration of 2 mM in a single dose, or with five daily doses of MNUA at concentrations of 0.2 mM. Tumor growth, or biological transformation, was seen only among cell lines grown in tissue culture for 14 or more wk before testing. Of these cell lines, one of five untreated lines underwent spontaneous transformation, three of six lines treated once with MNUA grew as tumors and five of six lines treated repeatedly with MNUA grew as tumors. Tumors developing were pleomorphic fibrosarcomas. The plating efficiency of MNUA-treated cells exceeded that of untreated cells by a factor of up to ten in all cases but one. All cell lines in which morphologically transformed colonies were seen grew as tumors when injected into irradiated mice. A search for murine leukemia virus in transformed cells was negative. It was suggested that malignant transformation is a stepwise process in which increased plating efficiency of treated cells appears first, followed by the appearance of morphologically transformed colonies and finally by the capacity to grow as tumors in irradiated hosts.



- 0969 8-HYDROXYQUINOLINE: CHRONIC TOXICITY AND INHIBITORY EFFECT ON THE CARCINOGENICITY OF N-2-FLUORENYLACETAMIDE. (E.) Yamamoto, R. S. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), M. Williams, H. H. Frankel and J. H. Weisburger. *Toxic Appl Pharmacol* 19(4):687-698, 1971.
- The effects of administering 8-hydroxyquinoline (HOQ) to six weeks old male Fischer strain rats for periods of up to 18 months on the incidence of neoplasia, and the effects of HOQ on the toxicity and carcinogenicity of N-2-fluorenylacetamide (FAA), were studied. HOQ caused rapid induction of hemosiderosis in the liver and spleen and eventually also in the heart, kidneys, testes, adrenal glands, pancreas, and thyroid. The iron deposition was excluded from the neoplastic cells of hepatomas and hyperplastic nodules in livers in which parenchymal cells contained heavy deposits. The control animals and those on HOQ alone showed no neoplastic lesions. It was found that HOQ reduced the toxicity of FAA. In addition administration of 0.08% HOQ together with 0.02% FAA led to a lower incidence of hepatic malignancies than when the carcinogen was fed alone in a time-limited test series. Reduction of the carcinogenicity of FAA was also reflected by increased survival time of rats fed HOQ together with the carcinogen compared to those fed the carcinogen alone. It was suggested that HOQ, like acetanilide, lowered the effective concentration of available N-hydroxy-FAA, the active intermediate required for expressing the carcinogenicity of aromatic amines such as FAA. HOQ is a phenolic compound which can act possibly by lowering the level of available sulfate, as does p-hydroxyacetanilide, previously indicated as the active ultimate carcinogen for rat liver derived from aromatic amines.
- 0970 MORPHOLOGY OF LUNG CANCER IN IRON ORE MINE WORKERS. (Rus.) Gurevich, M. A. (Krivoyog Res. Inst., U.S.S.R.) and N. Z. Slinchenko. *Arkh Patol Anat* 33(6):22-26, 1971.
- 0971 CYTOLOGICAL AND HISTOLOGICAL STUDIES OF THE VAGINAL AND UTERINE CERVIX UNDER CONDITIONS OF CONTRACEPTIVE INTAKE: PRELIMINARY COMMUNICATION. (Ger.) Dallenbach-Hellweg, G. (Heidelberg U., Germany), J. Herting, F. Momber and V. Thorn. *Fortschr Med* 9(32-33):883-887, 1971.
- 0972 AMINO-AZO-DYE-BINDING PROTEIN IN THE SOLUBLE CYTOPLASM OF THE RAT LIVER. (E.) Ketterer, J. (Courtauld Inst. Biochem., London, England) and J. Beale. *Biochem J* 122(5):53-54, 1971.
- 0973 RENAL PELVIC CARCINOMA IN PHENACETIN ABUSERS. (E.) Hoybye, G. (Frederiksberg Hosp., Copenhagen, Denmark) and O. E. Nielsen. *Scand J Urol Nephrol* 5(2):190-192, 1971.
- 0974 HAEMATOLOGICAL EFFECTS OF CHRONIC BENZENE POISONING IN 217 WORKERS. (E.) Aksoy M. (Istanbul Med. Sch., Turkey), K. Dincol, T. Akgün, M. Erdem and G. Dincol. *Brit J Industr Med* 28:296-302, 1971.
- 0975 ACUTE SYNERGISTIC TOXICITY AND HEPATIC NECROSIS FOLLOWING ORAL ADMINISTRATION OF SODIUM NITRITE AND SECONDARY AMINES TO MICE. (E.) Asahina, S. (Harvard Med. Sch., Boston, Mass.), M. A. Friedman, E. Arnold, G. N. Millar, M. Mishkin, Y. Bishop and S. S. Epstein. *Cancer Res* 31:1201-1205, 1971.
- 0976 EFFECT OF ESTRADIOL ON 7,12-DIMETHYLBENZ(a)ANTHRACENE-INDUCED ADRENOCORTICAL NECROSIS: A HISTOCHEMICAL STUDY. (E.) Horvath, E. (Inst. Exp. Med. Surg., U. Montreal, Canada), A. Somogyi and K. Kovacs. *Arch Geschwulstforsch* 37(3):203-209, 1971.
- 0977 THE RADIOLOGICAL INVESTIGATION OF THE EARLY MANIFESTATIONS OF EXPOSURE TO ASBESTOS DUST. (E.) MacKenzie, F. A. F. (Roy. Naval Hosp., Plymouth, England). *Proc Roy Soc Med* 64(8):834-837, 1971.
- 0978 VARIOUS N-METHYL-N-NITROSOUREA-INDUCED EFFECTS IN RATS: II. FERTILITY DISORDERS AND MALFORMATIONS. (Ger.) Kupfer, M. (Karl Marx U., Leipzig, Germany) and G. Kupfer. *Zbl Allg Path* 114(4):458-475, 1971.
- 0979 AUTORADIOGRAPHIC DEMONSTRATION OF 3-HYDROXYANTHRANILIC ACID-(<sup>3</sup>H) IN URINARY BLADDERS OF RATS BEFORE AND AFTER BILATERAL NEPHRECTOMY: A CONTRIBUTION TO THE ETIOLOGY OF VESICAL CARCINOMA. (Ger.) Hochberg, K. (Surg. Clin., U. Heidelberg, Germany), W. Kochen, L. Röhl and A. Porep. *Urol Int* 25(5-6):502-510, 1971.
- 0980 RAT LIVER GLYCEROLPHOSPHATE DEHYDROGENASES: ACTIVITY CHANGES AND INDUCTION BY THYROID HORMONE OF THE MITOCHONDRIAL ENZYME IN HEPATOMAS AND IN PRECANCEROUS AND GROWING LIVER. (E.) Karsten, U. (German Acad. Sci., Berlin-Buch), G. Sydow, A. Wollenberger and A. Graffi. *Acta Biol Med German* 26(6):1131-1140, 1971.
- 0981 COMPARATIVE STUDY OF METABOLIC PROFILES OF PRIMARY HEPATOMA, REGENERATING LIVER, AND LIVER IN NEWBORN SWISS MICE. (E.) Bhide, S. V. (Cancer Res. Inst., Bombay, India). *J Nat Cancer Inst* 47(4):797-800, 1971.
- 0982 BLADDER CANCER DUE TO EXPOSURE TO PARA-AMINOBIPHENYL: A 17-YEAR FOLLOWUP. (E.) Melick, W. F. (St. Louis U. Sch. Med., Mo.), J. J. Naryka and R. E. Kelly. *J Urol* 106(2):220-226, 1971.
- 0983 FLOOR TILE INSTALLATION AS A SOURCE OF ASBESTOS EXPOSURE. (E.) Murphy, R. L. (Harvard Med. Sch., Boston, Mass.), B. Levine, F. J. Al Bazzaz, J. J. Lynch and W. A. Burgess. *Amer Rev Resp Dis* 104(4):576-580, 1971.
- 0984 X-RAY DIAGNOSIS OF CANCER IN THE GLANDULAR STOMACH OF RATS. (E.) Kurihara, M. (Natl. Cancer Ctr., Tokyo, Japan), H. Ichikawa, S. Fujimura and T. Sugimura. *Gann* 62:225-229, 1971.

- 0985 THE QUESTION OF ISONIAZIDE (INH)-INDUCED BRONCHIAL AND SKIN CARCINOMAS EXEMPLIFIED BY LUPOUS TUBERCULOSIS. (Ger.) Jung, H.-D. (Reg. Ctr. Tuberculosis Lung Dis., Neubrandenburg, Germany). *Z Tuberk* 135(1):31-38, 1971.
- 0986 TESTICULAR CHORIOCARCINOMA IN LSD USERS: COINCIDENCE OR CAUSE? (E.) Levick, L. J. (Albert Einstein Med. Ctr., Philadelphia, Pa.) and S. N. Levick. *JAMA* 217(4):475-476, 1971.
- 0987 FINE STRUCTURE OF 7,12-DIMETHYLBENZ(a)-ANTHRACENE-INDUCED RHABDOMYOSARCOMA IN SYRIAN HAMSTERS. (E.) Markov, D. V. (Bulgarian Acad. Sci., Sofia, Bulgaria) and D. C. Hadjiolov. *Arch Geschwulstforsch* 37(4):344-351, 1971.
- 0988 BACTERIAL BIOSYNTHESIS OF POLYCYCLIC HYDROCARBONS OF THE 3,4-BENZOPYRENE TYPE IN LIVING SYSTEMS. (Fr.) Mallet, L. (No affiliation). *Gaz Hosp* 143(19-24):605-607, 1971.
- 0989 ALBUMIN-AFLATOXIN B<sub>1</sub> INTERACTIONS: CHROMATOGRAPHIC STUDIES BY MEANS OF THE FRONTAL ELUTION METHOD. (It.) Scoppa, P. (Euratom-ISPRA C.C.R., Naples, Italy) and W. O. Borle. *Boll Soc Ital Biol Sper* 47(7):201-205, 1971.
- 0990 ALBUMIN-AFLATOXIN B<sub>1</sub> INTERACTIONS: SPECTROPHOTOMETRY BY MEANS OF DIFFERENTIAL SPECTRA. (It.) Scoppa, P. (Euratom-ISPRA C.C.R., Naples, Italy) and E. Marafante. *Boll Soc Ital Biol Sper* 47(7):198-201, 1971.
- 0991 PREVENTIVE MEDICAL RECOMMENDATIONS FOR THE HANDLING OF CHEMICAL CARCINOGENS: PROBLEMS OF OCCUPATIONAL PROTECTION. (Ger.) Teichmann, B. (German Acad. Sci., Berlin), W. Gibel, T. Schramm and K. Lohs. *Arch Geschwulstforsch* 37(4):313-326, 1971.
- 0992 DIFFERENTIAL STAINING OF PRENEOPLASTIC FOCI IN RAT LIVER PARENCHYMA DURING AZO DYE CARCINOGENESIS. (E.) Briere, N. (Fac. Med., U. Sherbrooke, Sherbrooke, Quebec, Canada). *Histochemie* 25(2):113-119, 1971.
- See also:
- \* (Rev): 0911, 0916, 0918, 0920, 0922
  - \* (Phys): 0993
  - \* (Immun): 1062
  - \* (Path): 1085, 1092



## PHYSICAL CARCINOGENESIS

MECHANISMS OF CARCINOGENESIS. (E.) Brues, A. M. (Ill. Regional Med. Program), D. C. and H. Auerbach. *Argonne Nat Lab Div Biol Med Ann Report* 1970:48-50.

Studies of carcinogenesis from localized irradiation are reported. In one study, hairless (hr) mice and their haired sibling were given 10 rats of  $\beta$ -radiation to the lower two-thirds of the body; groups of irradiated mice were painted three times for one yr with a mixture of phorbol esters A and a derivative of croton oil. Treatment with phorbol esters appeared to increase the incidence of skin carcinomas and sarcomas in both haired and hairless mice; tumors were more frequent following irradiation in hairless mice than in haired mice. In 136 hairless mice given irradiation but no phorbol esters, 16 skin carcinomas and 16 sarcomas developed, while in 49 haired mice given phorbol ester as well as irradiation, eight skin carcinomas and eight sarcomas developed. Seventy-five percent of tumors in mice given phorbol esters were in the painted area; only 10% of tumors in unpainted mice appeared in the corresponding area. In a related experiment, the earlier observation that castration of female rats affects the distribution of bone tumors following s.c. injection of  $^{239}\text{Pu}$  was reexamined. Tabulation of results failed to confirm that there is a difference in bone tumor incidence between intact and castrated rats. In a third study, calculations from published data on bone sarcoma induction in mice and dogs with embedded  $\beta$ -radiation sources ( $^{90}\text{Sr}$  and  $^{239}\text{Pu}$ ) were analyzed. (Previous reports indicated that the small dog fails to respond to embedded  $\beta$ -sources which induce s.c. tumors in rats.) Calculations showed that on the basis of radiation exposure to individual cell, dog cells were much less sensitive than mouse cells to the carcinogenic stimulus.

4 THE USE OF A CYTOGENETIC MARKER IN THE INVESTIGATION OF LEUKEMOGENESIS IN AKR MICE. (E.) Legrand, E. (Bergonie Foundation, Bordeaux, France) and J. F. Duplan. *Int J Cancer* 7(3):443-448, 1971.

Dynamics of bone marrow, thymus and lymph node regeneration, along with radiation-induced leukemogenesis in AKR mice, were studied using a chromosome marker. Mice of an AKR-T1ALD strain syngeneic with the AKR strain were exposed to a single irradiation of 850-900 r and other groups of the same strain were exposed to four irradiations of 175 r at 1-wk intervals. The irradiated mice were restored by treatment with bone marrow from AKR or from AKR-T1ALD mice four hr following single or last radiation exposure. Lymphatic leukemia induced by four radiation exposures could be distributed into three groups according to latency period: (1) early leukemias (30%) which appeared to be of either host, donor or mixed origin; (2) leukemia which developed between 180 and 220 days following exposure and seemed to originate from host cells; and (3) late leukemias which developed following a greater than 220-day latency period and appeared to be of donor origin. Anomalies in the bone marrow, thymus and lymph node regeneration kinetics previous to first al-

terations due to the leukemic process were found at the cytogenetic level. Exposure to single dose irradiation followed by restoration produced leukemia which originated exclusively from donor cells. Conclusions as to the mono- or multifocal origin of leukemia could not be drawn. The equal probability in development of AKR or AKR-T1ALD leukemia indicated an equal susceptibility of both cell types to the Gross virus.

0995 FOREIGN BODY TUMORIGENESIS: TIMING AND LOCATION OF PRENEOPLASTIC EVENTS. (E.)

Brand, K. G. (Coll. Med. Sci., U. Minnesota, Minneapolis), L. C. Buoen and I. Brand. *J Nat Cancer Inst* 47(4):829-836, 1971.

Plastic, and occasionally glass, coverslips were inserted s.c. into the flanks of congenic Harwell mice strains CBA/H, CBA/H-T6, and their hybrids, and strain CBA/B-A and their hybrids with CBA/H. Preneoplastic cells were shown to be present at the site of foreign body reaction within one month of initial implantation. At this stage, the preneoplastic cells were either single or already existing in small clones. When clones were present, clonal progeny were demonstrated at first in the capsular and the extracapsular tissues, and later within the capsule tissue and directly on the implant surface. Segments of implants and surrounding tissue capsules that resulted from foreign body reaction were transplanted into recipient animals at various time intervals. These animals had cells containing the T6-marker chromosome, and so the implanted tissue was distinguishable from the secondary carriers. Animals and controls that experienced no transfer were monitored for tumor formation; both groups experienced tumor onset at about the same time, and in some instances, karyotypically homologous tumors were found in recipient mice. When data were plotted non-accumulatively against time, two peaks of tumor appearance became visible, followed by a third late peak. It is proposed that two or three classes of parent cells exist, and although they appear simultaneously at the implant site, they and their clonal offspring vary in the amount of time needed to complete preneoplastic maturation. In addition, it was noted that preneoplastic cells in females have a shorter latency period than that in male mice.

0996 THE METABOLISM OF TANTALUM IN THE RAT. (E.)

Fleshman, D. G. (Lawrence Rad. Lab., Livermore, Calif.), A. J. Silva and B. Shore. *Health Phys* 21:385-392, 1971.

0997 COMPARATIVE METABOLISM OF RADIONUCLIDES IN MAMMALS: VII. RETENTION OF  $^{106}\text{Ru}$  IN THE

MOUSE, RAT, MONKEY AND DOG. (E.) Furchner, J. E. (Los Alamos Sci. Lab., N. M.), C. R. Richmond and G. A. Drake. *Health Phys* 21:355-365, 1971.

0998 DEVELOPMENT OF A SOMATOTROPIC VARIANT OF THE MAMMOSOMATOTROPIC TUMOR MtT/W5 (35746).

(E.) Hollander, N. (Mount Sinai Sch. Med., New York, N.Y.) and V. P. Hollander. *Proc Soc Exp Biol Med* 137(4):1157-1162, 1971.

0999 KINETICS OF CALCIUM, STRONTIUM, BARIUM AND RADIUM IN RABBITS. (E.) Linkecki, J. (Inst. Med. Prac., Lodz, Poland). *Health Phys* 21:367-376, 1971.

1000 THE RESPONSE OF ANL BEAGLES TO PROTRACTED EXPOSURE TO  $^{60}\text{Co}$  GAMMA RAYS AT 5 TO 35 R/DAY: IV. BONE MARROW CELL ULTRASTRUCTURE IN DOGS CONTINUOUSLY EXPOSED TO  $^{60}\text{Co}$  GAMMA RAYS. (E.) Tahmisian, T. N. (No affiliation), R. L. Devine, W. P. Norris, R. E. Fritz, R. C. Zeman and D. V. Tolle. *Argonne Nat Lab Div Biol Med Res Ann Report* 1970:134.

1001 RETENTION OF RADIOSTRONTIUM IN SOFT TISSUES (E.) Brues, A. M. (Ill. Regional Med. Program), D. C. Grube and H. Auerbach. *Argonne Nat Lab Div Biol Med Res Ann Report* 1970:50-51.

See also;

- \* (Rev): 0915
- \* (Chem): 0941, 0970
- \* (Epid-Biom): 1104



2 DISSEMINATED RHABDOMYOSARCOMAS FORMED IN KITTENS BY CULTURED HUMAN RHABDOMYOSARCOMA (E.) McAllister, R. M. (U. Southern California Sch. Med., Los Angeles), W. A. Nelson-Rees, Y. Johnson, R. W. Rongey and M. B. Gardner. *Nat Cancer Inst* 47(3):603-611, 1971.

Transplantation of human cancer cells into cats is reported. Cells of a cultured human rhabdomyosarcoma (RD 1, line no. 2) were injected into fetuses of three pregnant cats at about 40 days gestation; 10<sup>7</sup> rhabdomyosarcoma cells were injected. Disseminated rhabdomyosarcomas were found in four kittens: two kittens from cat 1 and one kitten from cat 3. In addition, one full-term stillborn kitten from cat 2 had rhabdomyosarcomas in liver and thymus. Tumors were first seen at age 46 days and 60 days in kittens from cat 1, and at 55 days of age in the kitten from cat 3. Tumors in the four kittens were similar histologically and in fine structural appearance to those of human rhabdomyosarcoma from which the RD cell line is derived. C-type particles of unknown origin in association with sarcoma cells were seen in two kittens. The parent RD cell line contained no detectable C-type particles. Four cell lines were established by tumor cell isolation from three kittens' tumors. Each of the four cell lines consists of two cell types: plump polygonal cells, and long strap-shaped cells morphologically similar to those of the original human tumor. Four cell lines derived by isolation of strap cells from cat tumors contained metaphases with 42-100 chromosomes and resembled karyotypically cells of the human RD cell line. Tumor cell lines had a rapid generation time and a high saturation density; they formed colonies in agar and contained myoglobin. Tumor cell lines from cat tumors were inoculated into fetal kittens. Rhabdomyosarcomas formed in two of three surviving inoculated kittens 43 and 47 days after birth, resp.

03 PROTECTION OF MICE AGAINST GROSS LEUKEMIA BY INTERFERING ACTION OF NONLEUKEMOGENIC C-TYPE MURINE VIRUSES INOCULATED INTO NEWBORNS. (E.) M. R. S. (Gustave Roussy Inst., Villejuif, France), and J. K. Youn. *J Nat Cancer Inst* 47(3):575-583, 1971.

The interfering effect of nonleukemogenic C type murine viruses inoculated into newborn C3HeB/Fe mice on the production of leukemia is reported. A Gross leukemia virus (GV) type-specific, cell-surface antigen was shown by immunofluorescence to be present in cell lines having C-type virus particles. The two clonal cell lines, designated N1 and C19, which were chronically infected with abundantly replicating C-type virus particles, were inoculated into newborn mice four to five hr before challenge with highly leukemogenic passage A GV. Interference with leukemogenesis was particularly striking with the material from N1 cultures. Almost 60% of the mice had no leukemia during the 180-day observation period, as compared with 11% in the controls. Latency and survival time were prolonged in the leukemic mice. No interferon-like activity was observed in the plasma of mice inoculated with the material from N1 cultures. On the other hand, leukemogenesis was not significantly inhibited in

mice receiving an interferon inducer, polyinosinic: polycytidylic acid, before and after challenge with GV. Possible mechanisms involved in this interference phenomenon are a receptor blocking mechanism and a virus substitution mechanism.

1004 BIOGENESIS OF POXVIRUS: IDENTIFICATION OF FOUR ENZYME ACTIVITIES WITHIN PURIFIED YABA TUMOR VIRUS. (E.) Schwartz, J. (Publ. Hlth. Res. Inst., New York, N. Y.) and S. Dales. *Virology* 45(3):797-801, 1971.

A comparative study of the enzymatic complements of Yaba poxvirus and vaccinia virus is reported. DNase activities (acid and neutral), RNA polymerase activity and nucleotide phosphohydrolase (NPH) activity were investigated. DNase activity in Yaba virus was tested by incubating a purified suspension of stripped particles with native and denatured mammalian DNA. Native DNA was resistant to hydrolysis; however, single-stranded DNA was hydrolyzed readily. Two peaks of activity with pH optima at 5.0 and 7.8 (acid and neutral DNase, resp.) were evident. The specificity for single-stranded DNA and the pH optima of these activities were very similar to those seen with vaccinia and insect poxviruses, a finding which militated against the hypothesis that the absence of these DNases accounts for the oncogenicity of the Yaba agent. RNA polymerase assays showed that, in terms of kinetics of the reaction and in terms of specific activities, the Yaba-associated transcriptase was similar to the vaccinia enzyme. Yaba virus NPH activity also attained the same level, and had similar kinetics, to the NPH of vaccinia and insect poxviruses. The observations suggest that purified Yaba virus, like other poxviruses, contains at least 4 enzymatic activities. Among them, the RNA polymerase is undoubtedly related to the transcriptase from the coated genome of early RNA species required for the beginning of the infectious cycle.

1005 MATURE FORM OF THE DEOXYRIBONUCLEIC ACID FROM CHICK EMBRYO LETHAL ORPHAN VIRUS. (E.) Younghusband, H. B. (John Curtin Sch. Med. Res., Australian Natl. U., Canberra) and A. J. D. Bellett. *J Virol* 8(3):265-274, 1971.

The deoxyribonucleic acid (DNA) of chick embryo lethal orphan (CELO) virus, an oncogenic avian adenovirus, was studied to determine its similarity to bacteriophage DNA and to indicate possible relevance to the mechanism of viral oncogenesis. The Phelps strain of CELO virus was grown in chick embryo kidney monolayers by inoculating the cells with five to ten plaque-forming units of virus per cell. Before analysis, the viral DNA was purified and treated to prevent aggregation and disruption. Tests for base sequence heterogeneity, which include thermal denaturation profiles and densitometer tracing, showed that 53% of the regions of the molecule were composed of guanine-cytosine links and that an undetermined percentage contained adenine-thymine base pairs. The CELO virus DNA was then subjected to annealing conditions and sedimented in a sucrose gradient. It was determined that there was no difference in the sedimentation velocities of annealed and untreated DNA, although

ADNA formed circles under the same conditions. CELO virus DNA was tested for duplex terminal repetition by limited digestion with exonuclease III followed by annealing, acid-soluble radioactive labeling, and re-annealing. Radiographs indicated that the exonuclease III had removed nucleotides from 1 strand only at each terminus, but no circular molecules were found. Finally, when CELO virus DNA was sedimented, denatured, and annealed, all of the renatured molecules were linear, including some that were imperfectly renatured. The following conclusions can be drawn: DNA molecules of CELO virus contain regions of differing base composition; they have neither complementary single chain nor duplex terminal repetitions; they do not have regular single-strand interruptions of the type found in T5DNA; and they are a unique rather than permuted collection of sequences.

1006 AN IMPROVED *IN VITRO* ASSAY FOR CELL-FREE MAREK'S DISEASE VIRUS: BRIEF REPORT. (E.)

Addinger, H. K. (Albert Einstein Med. Ctr., Philadelphia, Pa.) and B. W. Calnek. *Arch Ges Virusforsch* 34(4):391-395, 1971.

This report describes the use of disodium ethylenedinitrilo tetraacetate (EDTA or Versene) in *in vitro* assays of cell-free Marek's disease virus (MDV) extracted from both the epithelial lining of feather follicles and chicken kidney cell (CKC) cultures. CKC cultures were prepared in 60 mm Petri plates and, when the cell sheet was 80% confluent, the drained, infected cultures were given increasing EDTA concentrations in inocula diluted either in phosphate buffered saline (PBS) or in a stabilizer containing sucrose, disodium glutamate, and bovine serum albumin in phosphate buffer (SPGA). The primary exposure was carried out at 38°C for a period of 30 min. Then the chelator was diluted approximately 20-fold for a secondary adsorption period of 20-24 hr. Alternatively, cultures were inoculated directly into maintenance media, thus avoiding the primary adsorption period. Six, eight and ten days postinoculation, focal lesions were counted microscopically, and the mean number from replicate cultures was used to calculate the focus forming units per ml (FFU/ml). The effect of the chelator was an increase of FFU with an increase of EDTA. This was verified by including appropriate controls in the assays, by fluorescence antibody tests on cells taken from birds that had been given intra-abdominal inoculations of cell-free virus, and by observing the development of lesions in live chicks that had been inoculated with CKC extract containing EDTA.

1007 HORMONE-ACTIVATED EXPRESSION OF THE C-TYPE RNA TUMOUR VIRUS GENOME. (E.) Hellman, A. (Natl. Cancer Inst., Bethesda, Md.) and A. Fowler. *Nature* 233(39):142-144, 1971.

To obtain experimental evidence that certain endocrines are capable of controlling gs expression of the C-type RNA tumor genome, NIH Swiss mice aged 21 days were divided into two groups; one group served as intact controls, while mice in the other group were bilaterally ovariectomized. Some mice from each group were then treated twice a wk with estro-

diol valerate (0.1 mg/0.1 ml) and/or hydroxyprogesterone caporate (0.1 mg/0.1 ml). Controls were sham injected with peanut oil. Uterus, spleen and thymus of treated and control mice were removed at 35, 42 and 56 days of age and extracts were prepared for gs assay. The gs assays were done with antisera prepared from rats carrying Moloney sarcoma virus-induced tumors. Expression of the gs antigen was prevented in uteri of 56-day-old mice by ovariectomy before sexual maturity. However, ovariectomized mice treated with estrogen during the prepubertal period did express gs antigenicity. The effect of progesterone and progesterone-estradiol combinations was less clear. Progesterone treatment in some cases seemed to suppress gs antigenicity expression. The observation of gs enhancement by certain steroids raised questions about the role of hormones acting as primary host cell regulators of oncogenic expression.

1008 DETECTION OF REPLICATING C-TYPE VIRUSES IN CONTINUOUS CELL CULTURES ESTABLISHED FROM COWS WITH LEUKEMIA: EFFECT OF THE CULTURE MEDIUM. (E.) Ferrer, J. F. (Sch. Vet. Med., U. Pennsylvania, Kennett Square), N. D. Stock and P. Lin. *J Nat Cancer Inst* 47(3):613-621, 1971.

The presence of C-type virus particles in four long-term suspension cultures (NBC cells) of buffy-coat or thoracic-duct lymphocytes of leukemic cows is reported. C-type particles appeared in NBC cell lines when cultured in a medium different from that in which they were normally cultured. NBC cell lines had been maintained in culture for about three years at the time of the study in McCoy's 5A medium supplemented with 20% heat-inactivated horse serum (medium M20HSI). To reproduce the experimental conditions under which virus-like particles (VLP) were found in short-term buffy-coat cultures of cows with leukemia, NBC cells were transferred from medium M20HSI to Eagle's minimal essential medium (modified) supplemented with 20% heat-inactivated fetal calf serum (medium E20FSI). C-type VLP were readily detected in samples from three of the four NBC cell cultures. Only in one cell line did addition of PHA to medium significantly increase the number of detectable VLP. Mature and immature VLP occurred extracellularly and within cytoplasmic vacuoles; mature C-type particles were usually circular and contained a central electron-dense nucleoid surrounded by a unit membrane. Distinct and typical budding forms of particles were frequent, often in association with free particles. Cylindrical or tubular buds were also present. In a separate examination, budding and mature C-type VLP were found in an M20HSI NBC culture, but to a lesser extent than in the E20FSI culture.

1009 LEUKAEMIA VIRUS-INDUCED ALTERATION OF LEUCOCYTE MIGRATION *IN VITRO*. (E.) Friedman, H. (Einstein Med. Ctr., Philadelphia, Pa.) and W. S. Ceglowski. *Nature* 233(5319):415-416, 1971.

An investigation of the effects of Friend leukemia virus (FLV) infection on the *in vitro* migration pat-



of lymphoid cells from various organs of the B/c mouse is reported. Spleens and other lymphoid tissues from FLV-infected and uninfected mice were excised, centrifuged, and placed in Sykes-Moore chambers. The areas of migration from capillary tubes of cells from infected and uninfected mice were determined. The area of migration from spleen cells of infected mice decreased considerably with time after infection. When infection occurred two to three days before death, the migration area was 10-20% smaller than that of the uninfected controls. The inhibition of *in vitro* migration of spleen cells was directly related to the dose of infecting virus; the decrease of migration activity was less pronounced when serial dilutions of virus were used for infection. Migration of cells from superficial and deep lymph nodes, thymus and bone marrow was not depressed during the first seven to ten days after FLV infection. After two to three weeks postinfection, however, lymph node and bone marrow cells migrated less actively than the same cells from uninfected control mice.

10 RELATIONSHIP BETWEEN THE SYNTHESIS OF EPSTEIN-BARR VIRUS AND GROWTH OF HOST CELL  
A BURKITT LYMPHOMA CELL LINE, P3HR-1 (E.) Sairen-T. (Tohoku U. Sch. Dent. Sendai, Japan), and Y. Iizuma. *Gann* 10:113-122, 1971.

Studies on the relationship between Epstein-Barr (EB) virus and host cell growth in the P3HR-1 Burkitt lymphoma line are presented. The rate of DNA synthesis was determined by measurement of  $^3\text{H}$  thymidine incorporation. Autoradiography and cell synchronization were carried out. During the logarithmic growth of the cell population an increase of EB virus antigen-bearing cell fraction indicated that at least part of the virus-bearing cells was capable of dividing but with a lower growth rate than the antigen free cells. Thus, a continuous decline of the virus-bearing cell fraction may occur in the logarithmic growth of the other population of cells. Pretreatment with hydroxyurea or with excess thymidine gave results suggesting a possible correlation between the EB virus growth and the particular phase in the cell cycle. Colcemid, a known blocking agent to mitotic division, was tested to see whether it would affect the EB virus replication when host cell division was inhibited. The presence of 0.1  $\mu\text{g}/\text{ml}$  of colcemid resulted in an increased percentage of EB virus antigen-bearing cells. The effect of the addition of colcemid (0.1  $\mu\text{g}/\text{ml}$ ) on the synthesis of EB virus in cells pretreated with hydroxyurea and released from it gave results which indicated that this procedure could synchronize a portion of the cells in a given culture and enhance the synthesis of EB virus antigen which was further accelerated by the addition of colcemid.

11 LARGE-SCALE PRODUCTION OF BURKITT LYMPHOMA CELLS AND EB VIRUS IN TISSUE CULTURES. (E.) Hansen, E. M. (Pfizer Inc., Maywood, N.J.), F. T. Busch and D. Riccardo. *Gann* 10:123-133, 1971.

A procedure for the large-scale production of Burkitt's lymphoma cells and EB virus in tissue culture is described. Fermentors, used earlier for virus production, are used in the production of large quantities of pri-

mate lymphocytes, an important source of the EB virus. The lymphocytes were then plated out in shallow, stationary flask cultures which are more conducive to high virus yield. The virus content of the preparation was monitored routinely by electron microscopy using a semi-quantitative method of phosphotungstic acid negative staining. The cultured cells and medium were harvested and viruses were collected by a continuous flow density gradient system.

1012 COVALENTLY LINKED RNA-DNA MOLECULE AS INITIAL PRODUCT OF RNA TUMOR VIRUS DNA POLYMERASE. (E.) Verma, I. M. (Dept. Biol., Massachusetts Inst. Tech., Cambridge), N. L. Meuth, E. Bromfield, K. F. Manly and D. Baltimore. *Nature* 233(39):131-134, 1971.

An investigation of the RNA-dependent DNA polymerase of avian myeloblastosis virus (AMV) using endogenous RNA template is reported. In previous experiments with the endogenous DNA polymerase reaction of Moloney murine leukemia virus (MLV), it had been established that the initial product of MLV polymerase is a covalently bonded DNA-RNA molecule. The endogenous product of the AMV polymerase reaction formed after 2, 5, 10, 15 and 30 min of reaction was banded in  $\text{Cs}_2\text{SO}_4$  in its native state, after boiling and alkali treatment. The heat-denatured product after two min of incubation banded heterogeneously with most of the DNA heavier than 1.5 g/ml (the density of a 1:1 DNA-RNA hydrogen-bonded duplex). Treatment of the AMV DNA polymerase products with alkali in conditions which hydrolyze all RNA caused them to band in  $\text{Cs}_2\text{SO}_4$  at a lower average density than the boiled product. After boiling treatment, almost all of the DNA remained in a single-stranded state. The product formed when purified enzyme was allowed to copy 60-70S viral RNA behaved similarly to the product of the endogenous reaction; this finding supported the idea that these two systems were comparable. The data indicated that the initial product of the endogenous DNA polymerase reaction of both AMV and MLV, and of the reaction of purified AMV polymerase with AMV 60-70S RNA, was a covalently bonded DNA-RNA molecule. Covalent bonding was indicated by the resistance of the product to boiling. The RNA in the product presumably acted as a primer for the endogenous reaction.

1013 CORRELATION BETWEEN HUMORAL ANTIBODY AND REGRESSION OF TUMOURS INDUCED BY FELINE SARCOMA VIRUS. (E.) Essex, M. (Karolinska, Inst., Stockholm, Sweden), G. Klein, S. Snyder and J. Harrold. *Nature* 233(5316):195-196, 1971.

A correlation was established between the presence of humoral antibodies to virus-associated cell membrane antigens and the failure of cats injected with feline sarcoma virus (FSV) to develop progressive malignant tumors. A lymphoblastoid cell culture derived from feline leukemia virus (FeLV)-induced tumor provided target cells. An indirect membrane immunofluorescence technique was used. Fluorescein-conjugated antiserum to cat IgG was used in a 1:20 dilution. Twenty-one cats which were 0-1, 4, 13, 26 and 52 weeks old received 1.0 g equivalents of FSV. A distinct

negative correlation was seen between the antibody titer three to seven wk after FSV inoculation and the development of progressive tumors. Of three cats which were injected with FSV at one yr of age, two failed to develop palpable tumors and one developed a tumor which subsequently regressed. All three developed antibody titers which ranged from 16 to 256. When all age groups are considered, nine cats developed tumors which were classed as progressive. Of these nine, none developed antibody titers above two, and five had no demonstrable antibody. Twelve cats either developed no tumor or developed antibody titers of four or higher, and eight had titers of at least 16. The findings clearly demonstrate an association between the development of antibody titres and either tumor regression or the lack of palpable tumor development. They also demonstrate a reaction between antibody associated with injections of FSV and a cell membrane antigen of cells that produce FeLV.

1014 ST FELINE SARCOMA VIRUS: BIOLOGICAL CHARACTERISTICS AND *IN VITRO* PROPAGATION.

(E.) Sarma, P. S. (Nat'l. Cancer Inst., Bethesda, Md.), T. Log and G. H. Thielen. *Proc Soc Biol Med* 137(4):1444-1448, 1971.

Some biological characteristics of the Snyder-Theilen strain of feline sarcoma virus (ST-FSV) are reported; the ST-FSV was isolated originally from a naturally occurring fibrosarcoma of a two year old cat. Concentrates of experimentally induced ST-FSV sarcoma induced morphologic transformation of feline embryo fibroblast FEF cells. Cell transformation effects were reproducibly induced in FEF cultures by serial passage of clarified culture fluids of infected FEF cultures. Examination of ST-FSV-inoculated FEF cultures for feline C-type virus showed that virus stocks contain a  $1-3 \log_{10}$  excess of a noncytopathogenic virus. Serial passage of fluids containing complement-fixing viral antigen resulted in the isolation of a feline C-type virus with properties identical to the noncytopathogenic feline leukemia virus. Focus assays in feline embryo cultures gave "non-defective" "one-hit" titration patterns. A potent dog antiserum against the Gardner-Arnstein strain of FSV (GA-FSV) neutralized ST-FSV; this suggested that ST-FSV is antigenically related to GA-FSV, a member of subgroup B of the feline sarcomas complex. Intramuscular inoculation of the culture fluid of the 4th FEF tissue culture passage of ST-FSV into 5-day-old kittens resulted in the production of progressively growing and fatal fibrosarcomas in all inoculated kittens. ST-FSV was similar to GA-FSV in its ability to transform heterologous mammalian cells. The ST-FSV propagated in FEF culture replicated and induced morphologic transformation of secondary whole embryo cultures of human, canine and porcine origin.

1015 THE DNA OF MURINE SARCOMA-LEUKEMIA VIRUS.

(E.) Biswal, N. (Baylor Coll. Med., Houston, Texas), B. McCain and M. Benyesh-Melnick. *Virology* 45(3):697-706, 1971.

Experiments designed to isolate and characterize the nucleic acid in the virions of each of three different

oncogenic RNA viruses are described. Murine sarcoma-leukemia virus complex (MSV-MLV), Rauscher leukemia virus (RLV), and avian myeloblastosis virus (AMV) were used and the nucleic acids were isolated from the purified virions. The method for obtaining thymidine- $^3\text{H}$ -labeled purified DNA and its incorporation into MSV-MLV is described. The presence of DNA in the three types of virus was demonstrated and equilibrium centrifugation experiments revealed four distinct sedimenting species of nucleic acid: one with a buoyant density of 1.423, characteristic of DNA, and other three with densities characteristic of RNA. The DNA made up 2.5% of the total nucleic acid content of virions and resolved into two components with buoyant densities of 1.698 and 1.678, resp. in CsCl gradients. It is suggested that the DNA may be an integral part of the viral genome responsible for initiation and maintenance of cell transformation, that the DNA of the transformed cell may have been incorporated into the virions during maturation, and that this DNA has complementarity with the viral DNA.

1016 PROTEIN KINASE AND PHOSPHATE ACCEPTOR PROTEINS IN RAUSCHER MURINE LEUKAEMIA VIRUS.

(E.) Strand, M. (Albert Einstein Coll. Med., Bronx, N.Y.) and J. T. August. *Nature* 233(39):137-140, 1971.

The presence of a protein kinase in purified preparations of Rauscher murine leukemia virus (R-MLV) as well as in other membrane maturing viruses is reported, and the phosphorylation by this enzyme of several proteins of the virion is described. The incorporation of  $^{32}\text{P}$  into acid insoluble material was detected when R-MLV was incubated in the presence of labeled ATP in the absence of any added non-viral protein. This incorporation was markedly increased by the addition of protamine, arginine or lysine-rich histones. A protein isolated from *E. coli* increased the incorporation tenfold. Even in the absence of added proteins  $^{32}\text{P}$  is incorporated into an acid insoluble form which suggests that the virus contains substrate proteins as well as a protein kinase. This was confirmed by chemical analysis of the reaction product. About 30 separate peptides could be resolved from 120  $\mu\text{g}$  virus protein by use of a high resolution sodium dodecyl sulfate poly-acrylamide gel, and at least ten of the virus proteins were labeled with  $^{32}\text{P}$ . The experiments demonstrate the presence, in both oncogenic and normal membrane maturing viruses, of a protein kinase which phosphorylates the major structural proteins of the virion. It is suggested that the virus itself may be subject to regulation by the host cell.

1017 THE STRUCTURE AND ASSEMBLY OF MURINE LEUKEMIA VIRUS: INTRACELLULAR VIRAL RNA. (E.)

Watson, J. D. (Salk Inst., San Diego, Calif.). *Virology* 45(3):586-597, 1971.

A method for the isolation of murine leukemia virus (MLV) RNA in a sub-unit form from the cytoplasm of infected cells is described and the cytoplasmic component is compared to that found in the extracellular virion. Cells were grown in Eagle's medium supplemented with calf serum and  $\text{CO}_2$ , radioactively labeled with uridine- $^3\text{H}$ . The RNA from virions and from cells was purified and fractionated in sucrose gradients



ng dimethyl sulfoxide (DMSO). Polyacrylamide gel electrophoresis was carried out and RNA base compositions were determined. The large viral RNA component was converted by the DMSO treatment to a homogeneous form with a sedimentation rate of 38 S and a molecular weight of  $3.6$  to  $4.0 \times 10^6$  daltons. When it was incubated at  $37^\circ$  for three to six hr, multiple sedimenting forms were seen; this was also seen in the DMSO-treated 70 S RNA prepared from MLV radioactive-labeled for long periods. The large viral RNA component could not be detected in MLV-infected cells, when cytoplasmic RNA was treated with DMSO and density velocity sedimentation was used, an RNA component was isolated which had a similar electrophoretic mobility and base composition to 38S viral RNA; this fraction represented 0.1-0.4% of the total cytoplasmic RNA. Specific membrane regions appear to be involved as leukemia virion assembly sites and the assembly process appears to involve the transportation and packaging of the subunits into the 70S structure.

18 MURINE LEUKEMIA VIRUS: HIGH-FREQUENCY ACTIVATION *IN VITRO* BY 5-IODODEOXYURIDINE AND 5-BROMODEOXYURIDINE. (E.) Lowy, D. R. (Nat'l. Inst. Allergy Infec. Dis., Bethesda, Md.), W. P. Anderson, N. Teich and J. W. Hartley. *Science* 174(4005): 5-156, 1971.

Studies of the activation of murine leukemia virus (MLV) in cell lines of high leukemic AKR mice are reported. Two cell lines of AKR embryos were grown in culture as virus-negative cell lines. These cells gave no evidence of MLV expression in extensive testing for infectivity, viral antigens, morphologic alterations or reverse transcriptase activity. Exposure of these cells to 5-iododeoxyuridine (IUDR) or 5-bromodeoxyuridine (BUDR) consistently and rapidly induced MLV synthesis in a relatively high proportion of the previously virus-negative cells. Exposure of growing cultures to 20 or 100  $\mu$ g IUDR or BUDR/ml for 24-48 hr induced synthesis of MLV by as many as 0.5% of the cells within one wk after addition of the drug, an increase of about  $10^6$  times over the spontaneous rate of virus synthesis. Induction of MLV by IUDR and BUDR appeared to require incorporation of the drugs into DNA. When cultures that had been exposed to a suboptimum dose of BUDR were subsequently irradiated with high-intensity visible light, the activation rate of MLV was increased. The results suggest that the complete MLV genome is present in all AKR cells, and that the genome can be present without detectable expression as antigen or C-type particles.

19 NUCLEIC ACID SYNTHESIS IN HeLa CELLS INFECTED WITH TYPE 10 ADENOVIRUS: I. INCORPORATION OF THYMIDINE  $^3$ H. (E.) Semkow, R. (State Inst. Hyg., Warsaw, Poland) and T. Majle. *J. Med. Microbiol.* 22(4):339-344, 1971.

The time course of tritiated thymidine incorporation into HeLa cells infected with type 10 adenovirus is reported. Incorporation of thymidine  $^3$ H, measured autoradiographically, was found to be higher in infected cells than in controls. The percent of heavily labeled cells decreased in control and

increased in infected cells. This shift of label intensity took place progressively from the time of infection to the end of the 20 h experiment. These results agree with biochemical determinations of adenovirus infected cells in which the level of DNA is thought to increase in the course of infection.

1020 VIROLOGICAL AND IMMUNOLOGICAL CHARACTERISTICS OF HERPES-TYPE VIRUS ISOLATED FROM CHICKEN WITH MAREK'S DISEASE USING DUCK EMBRYO FIBROBLAST CULTURE. (E.) Kato, S. (Res. Inst. Microbial Dis., Osaka U., Japan), K. Ono, M. Naito, S. Tanabe, T. Onoda, Y. Mori, T. Doi and N. Iwa. *Gann* 10:91-107, 1971.

A report dealing with the isolation and with some virological characteristics of chick-herpes-type virus with reference to immunological relationships between that virus and EB virus is presented. Cytopathic agents were isolated from chickens with Marek's disease and serially passaged in duck embryo fibroblast (DEF). The cytopathic effect was characterized by foci and refractile rounded or shrunken cells; these foci were seen as microplaques in DEF cultures. Chickens inoculated with DEF-passaged herpes-type virus did not show any incidence of Marek's disease, but those inoculated with blood of Marek's disease chicken showed a high incidence of this disease. A linear relationship was found between the number of foci formed and dilution of the inoculum of chick herpes-type virus upon examination of the microplaques from the virus-infected DEF. The number of microplaques in infected quail fibroblasts was the same as in the DEF, but quail fibroblasts were found to be less susceptible to chicken herpes-type virus. Anti-herpes-type titers in chick sera showed antibody activity in apparently healthy chickens except for those raised in plastic containers. It was found that at least one antigen of the herpes-type is identical with that of the EB virus from Burkitt's lymphoma. Mitotic figures and  $^3$ H-thymidine incorporation were rarely found in foci of herpes-type virus-infected duck and quail fibroblast cultures; this indicated that the cells in the foci were not transformed but were degenerated.

1021 TRANSFORMATION OF THE CULTURED CELL SHEETS OF NASOPHARYNGEAL CARCINOMA BY EXTRACTS OF P3HR-1 AND NPC-204 CELLS CARRYING HERPES-TYPE VIRUS. (E.) Takada, M. (Kitasato Inst., Tokyo, Japan), A. Kawamura, Jr. and H. Sugano. *Gann* 10:163-171, 1971.

A study, designed to demonstrate infectivity and transforming ability of the herpes-type virus present in the NPC-204 and P3HR-1 floating cell cultures on the nasopharyngeal carcinoma culture cell sheets, is presented. These cell sheets were obtained from cultured cells derived from biopsy materials of nasopharyngeal carcinoma patients; herpes-type virus particles were not detected in these cells before being infected and transformed. The cell sheets were maintained under conditions unfavorable for the formation of the herpes-type virus for four weeks and were then exposed to the cell-free extract containing herpes-type virus. Inoculation of the cell sheets with extracts of NPC-204 and P3HR-1 resulted in morphologically distinct cell transformation when incubated, rounded

cells appearing on the cell sheets on the 22nd day after inoculation. It was possible to establish long term culture of the floating cells and three cell lines were established *in vitro* by transformation.

- 1022 STUDIES ON THE CHARACTERISTICS OF A HERPES-TYPE VIRUS ISOLATED FROM A CHICKEN WITH MAREK'S DISEASE. (E.) Onoda, T. (Res. Fdn. Microbial Dis., Osaka U., Japan), K. Koyama, T. Konobe, K. Takaku, K. Ono and S. Kato. *Biken J* 14(2):167-176, 1971.

Characterization of a herpes-type virus (HTV) (Biken C strain) isolated from a chicken with Marek's disease was performed. Serial passage in duck embryo fibroblasts (DEF) or quail embryo fibroblasts (QUEF) cultures showed a gradual increase in the rate of development of plaques of HTV. By the 100th passage, large plaques were produced in both lines. DEF showed larger syncytia than QUEF. Equal susceptibility to QUEF passaged-HTV was shown in both lines but DEF was more susceptible to DEF passaged-HTV. QUEF passaged-HTV after five passages in DEF cultures maintained its characteristics. DEF or QUEF passaged-HTV demonstrated no pathogenicity even after long term culture. Reisolation of the virus from chickens inoculated with either DEF passaged-HTV or QUEF 13 weeks following inoculation was accomplished. DEF passage-HTV was reisolated less frequently when the inoculation used was a virulent HTV (Biken VI strain) no evidence of reversion to the original type virus was noted in the reisolated HTV. The size and morphology of the plaques of HTV along with its infectivity to QUEF and DEF could be useful virological markers of HTV.

- 1023 ESTABLISHMENT OF LYMPHOBLASTOID, FLOATING CELL LINE FROM ADENOID TISSUE WITH ABNORMAL VEGETATION, AND PRESENCE OF HERPES-TYPE VIRAL ANTIGEN. (E.) Hosokawa, T. (Nagoya City U. Med. Sch., Japan), A. Ishimoto, Y. Ito and T. Takasu. *Gann* 10:209-212, 1971.

An unusual distribution of high antibody titer against herpes-type virus in connection with abnormal adenoid vegetation is reported together with the detection of herpes-type virus antigen in a newly established lymphoblastoid cell line from this adenoid tissue. The results are based upon 18 adenoid tissue specimens and sera from patients with abnormal adenoid vegetation. Biopsy specimens of adenoid tissue from patients with high antibody titers revealed fibroblastic growth in cultures and free-floating cells, consisting of lymphoblastoid cells and a few giant cells. The results suggest a possible influence of herpes-type virus on the adenoid and the role of this virus as an etiological agent in the cause of Burkitt lymphoma, nasopharyngeal cancer and infectious mononucleosis.

- 1024 COMPARATIVE SEQUENTIAL CYTOLOGIC CHANGES FOLLOWING IN VITRO INFECTION WITH HERPES-VIRUS TYPES I AND II. (E.) Teplitz, R. L. (City of Hope Natl. Med. Ctr., Duarte, Calif.), Z. Valco and T. Rundall. *Acta Cytol* 15(5):455-459, 1971.

An *in vitro* model system is used to examine the temporal pattern of events in herpes-virus infection of human cells. Cell cultures derived from a human skin biopsy, HeLa cells, and cells derived from a cervical carcinoma metastasis were infected with herpes simplex virus type I (HSV-type I) or herpes genitalis virus type II (HGV-type II). HSV-type I-infected cells did not differ from uninfected controls during the first 48 hr postinfection. By 72 hr, 80% of skin cells showed deep staining and opacification of cytoplasm; nuclei were enlarged and multinucleation was frequent. Cervical metastasis cells at 72 hr showed slight nuclear enlargement (35-50% of cells). HeLa cells at 72 hrs showed changes like those in cervical metastasis cells. By 96 hr postinfection, skin cells showed degenerative changes and granular cytoplasm appeared. Almost 100% of cervical metastasis cells were affected by 96 hr; nuclear vesiculation was marked and some intranuclear inclusion bodies were visible. Findings in HeLa cells at 96 hr were essentially an extension of findings at 72 hr. Cells infected with HGV-type II showed no changes at 24 hr postinoculation. By 48 hr skin cells showed eosinophilic homogenization of nuclear chromatin in less than 1% of cases. About 80% of cervical metastasis cells showed nuclear vesiculation with peripheral chromatin beading at 48 hr postinfection. HeLa cells at 48 hr showed loss of cytoplasm and loculation, homogenization and granulation of nuclei. At 72 hr, most skin cells were enlarged and showed eosinophilic nuclear granulation, together with increased multinucleation and degeneration of some cells. Cervical metastasis cells and HeLa cells at 72 hr showed extensions of changes seen at 48 hr. By 96 hr postinoculation, skin cells showed nuclear loculation, and cervical metastasis and HeLa cells showed extensive degenerative changes together with the cytologic changes already in evidence. Types I and II can be distinguished in tissue culture on the basis of nuclear loculation seen only in type II.

- 1025 SPECIFIC CHROMOSOME CHANGE IN INFECTION WITH HERPES-TYPE VIRUS *IN VITRO*. (E.) Yamamoto, K. (Hokkaido U. Sch. Med., Japan) and T. Osato. *Gann* 10:109-112, 1971.

A study is described which was designed to investigate chromosome changes in human cells shortly after infection with herpes-type virus *in vitro*. Virus was obtained from two human cell lines, THE-3 and P3HR-1; these lines were derived, resp., from cells transformed by human leukemic culture fluid, and Burkitt lymphoma cells. The virus-containing cells were inoculated in cultures of human female embryo tissues. Chromosome changes, involving chromatid breaks, iso-chromatid breaks, and secondary constrictions, became evident shortly after exposure of cells to virus. The incidence of metaphase plates with the chromosome changes in THE-3 cells was 35-40% after 7-24 hr post virus infection, decreasing to less than 20% thereafter. C-group chromosomes were affected preferentially; a subterminal secondary constriction in the no. 10 chromosome was especially prominent. To determine if viral synthesis was in-



d in the chromosomally-affected human embryo  
res exposed to herpes-type virus, immunofluores-  
examinations were performed; specific immuno-  
escence was not evident in tests using human  
which was immunoferritin-positive to herpes-  
virus particles.

CHARACTERISTICS OF THE STRUCTURAL COMPONENTS  
OF THE MOUSE MAMMARY TUMOR VIRUS: I. MOR-  
OLOGICAL AND BIOCHEMICAL STUDIES. (E.) Sarkar,  
(Sloan-Kettering Inst., New York, N.Y.), R. C.  
aski and S. H. Moore. *Virology* 46(1):1-20, 1971.

Isolation of the subviral components of the mouse  
ary tumor virus (MTV) is described. Milk from  
ed mice of strains susceptible to mammary tumors  
used as a source of virus. The virus was purified  
the use of different density gradient centrifuga-  
and, after treatment with Tween 80-ether, the  
ous extract was further purified and fraction I,  
aining viral nucleoids, some damaged virions,  
disrupted membranes, was separated from fraction  
Isolated viral nucleoids and purified MTV were  
ted with pancreatic ribonuclease. The buoyant  
ity of the nucleoid in potassium citrate or  
rate is  $1.24 \text{ g/cm}^3$  as compared to  $1.16\text{--}1.18 \text{ g/cm}^3$   
the untreated virus. In negatively stained  
arations the MTV nucleoids are pleomorphic with  
forms being spherical. The viral nucleoid  
ains 4.4% RNA and the intact virus shows 1.9% RNA.  
eoid capsules are resistant to protease and can  
isolated by density-gradient centrifugation; they  
the morphological appearance of empty bags, and  
ably contain either lipid or carbohydrate, since  
r density is  $1.14 \text{ g/cm}^3$ . The high degree of order  
pikes and the regular structure of the membrane  
est that the viral membrane has a characteristic  
etry that is distorted in preparation for electron  
oscopy.

INVESTIGATIONS OF THE ONCOGENIC ACTIVITY FOR  
THE CHICK EMBRYO OF RIBONUCLEIC ACID (RNA)  
TRACTED FROM FOWL SARCOMA INDUCED BY THE CARR  
IN (ZILBER) OF ROUS VIRUS. (E.) Nastac, E.  
S. Nicolau Inst. Virol, Bucharest, Rumania),  
lungu, E. Ursu and P. Athanasiu. *Rev Roum*  
*amicrobiol* 8(1):77-82, 1971.

carcinogenic activity of RNA extracted from fowl  
oma induced by Rous sarcoma virus, Carr-Zilber  
in, on the chorioallantoic membrane of embryonate  
s eggs is described. Tumoral suspensions, RNA  
tracts, viral suspensions, and RNase-treated RNA  
e prepared from Carr-Zilber Rous virus-induced  
ors and injected into the chorioallantoic mem-  
nes of seven-day-old chick embryos. Carr-Zilber Rous  
us RNA was oncogenic for the chorioallantoic  
brane; the oncogenic activity of RNA was compara-  
to the activities of tumor suspensions and viral  
pensions. Viral RNA produced fibrosarcomas in 19  
24 injected embryos, while tumoral suspension  
duced fibrosarcomas in 13 of 18 treated embryos  
viral suspension produced fibrosarcomas in 18 of  
treated embryos. The oncogenic activity of Carr-  
ber Rous virus RNA for the chick chorioallantoic  
brane was inhibited by treatment of the RNA extract

with RNase (none of 18 embryos given RNase-treated  
RNA developed fibrosarcomas).

1028 TUMOR PRODUCTION IN SQUIRREL MONKEYS (*Sai-  
miri sciureus*) BY ROUS SARCOMA VIRUS. (E.)  
Rabin, H. (Inst. Comp. Biol., San Diego, Calif.) and  
R. W. Cooper. *Lab Anim Sci* 21(5):705-711, 1971.

The production of tumors by Schmidt-Ruppin Rous sar-  
coma virus (RSV) in squirrel monkeys of several age  
classes is reported. Eleven monkeys ranging in age  
from newborn to four-yr-old were inoculated i.m. or s.c.  
with RSV preparations; the standard inoculum size  
equalled  $8 \times 10^6$  or  $3 \times 10^5$  tissue culture infectious  
U. All animals up to ten-mo.-old developed slow-growing  
tumors at the inoculation site after an average latent  
period of 37.2 days. Three adult monkeys older than  
four-yr-old were refractory to tumor formation. Of eight  
tumors produced, four regressed. The onset of regression  
occurred several wk after first appearance of tumor in  
three cases. Although distant metastases were not ob-  
served in the RSV-inoculated squirrel monkeys, tumors  
were classified as sarcomas on the basis of their in-  
filtrative growth and the anaplastic appearance of  
their cells. Extracellular virus-like particles re-  
sembling those typical of the avian leukosis group  
were seen in two tumors. The lowest tumor-producing  
doses of RSV corresponded to  $3 \times 10^3$  and  $8 \times 10^3$  in-  
fectious U of virus for tissue cultures of chick  
embryo fibroblasts. One male monkey aged more than  
five-yr-old, when treated with goat anti-squirrel mon-  
key thymocyte globulin, developed a tumor 35 days after  
RSV inoculation. Another male, also more than 5-yr-old,  
when treated with normal goat globulin, was refractory  
to RSV oncogenesis.

1029 ASSOCIATION BETWEEN PRODUCTION OF INFECTIOUS  
VIRUS AND CHROMOSOMAL ABERRATIONS IN CAR-  
CINOMATOUS HUMAN CELLS (HeLa) PERSISTENTLY INFECTED  
WITH PAPOVA VIRUS SV40. (E.) Nachtigal, M. (Acad.  
Med. Sci., Bucharest, Rumania), I. Aderca and M.  
Iftimovici. *Rev Roum Inframicrobiol* 8(2):91-99,  
1971.

An analysis of chromosomal changes in HeLa cells at  
different time intervals after exposure to SV40  
is reported; an increased level of chromosome aber-  
rations is associated with release of infectious  
SV40 by SV40-inoculated HeLa cells (designated L82  
cells). All cellular passages of the L82 cell line  
were tested for infectious SV40; virus was found in  
all passages. Cell lines obtained by cloning L82  
cells did not reveal infectious SV40. L82 cells  
were examined for chromosomes at passages 7, 9, 15,  
22 and 30 and a modal value of 64 chromosomes  
persisted throughout all the examinations. This  
was the same modal value as that of uninoculated  
HeLa cells (64-65 chromosomes). The frequency of  
L82 cells containing chromosome breaks was generally  
higher than the frequency of the corresponding  
uninoculated HeLa cells, but in passages 9 and 15  
of L82 cells, the difference in frequency of chro-  
mosomal breaks between L82 cells and uninoculated  
HeLa cells was not significant. The frequency of L82  
cells containing dicentrics was 21-34%, while the fre-  
quency of uninoculated HeLa cells and of cloned L82  
cells which contained dicentrics was 0-8%. In one

clonal subline derived from L82 cells, the modal chromosome number was 59; in this clonal subline and in one other clonal subline the level of cells with structural chromosome aberrations was similar to levels found in uninoculated HeLa cells.

- 1030 INDUCTION OF CELLULAR DNA SYNTHESIS DURING LYTIC INFECTION WITH SV40: A FUNCTION OF VIRAL GENOME. (E.) Brandner, G. (German Res. Inst., Freiburg), D. Boehlandt, J. Burger and M. Leveringhaus. *Archiv Ges Virusforsch* 34(4):323-331, 1971.

A study of the induction of cellular DNA replication is described which reveals its relationship to early SV40 genome expression. SV40 was inactivated with UV-light and AGMK cells were inoculated with this virus preparation. The synthesis of cellular DNA was studied by means of IUDR-labeling, in the presence of FUdR which blocks the endogenous thymidine pathway. The DNA inducing ability was shown to decrease with the decrease in infectivity of the virus preparation, UV-light-inactivated SV40 virus having no inducing ability. SV40 coat protein inoculation was also found to have no effect on DNA synthesis stimulation. SV40-infected cells pretreated with monkey interferon showed no increased DNA replication compared with non-infected cultures. No viral DNA was formed in infected cells pretreated with interferon. It is concluded that in lytic infections the hypothetical inducer is likely to be a newly synthesized product coded by the virus genome. This is supported by the failure of SV40 capsids or UV-light irradiated SV40 to stimulate cellular DNA synthesis.

- 1031 UNSCHEDULED DNA SYNTHESIS, U.V.-INDUCED CHROMOSOME ABERRATIONS AND SV<sub>40</sub> TRANSFORMATION IN CULTURED CELLS FROM XERODERMA PIGMENTOSUM. (E.) Parrington, J. M. (Galton Lab., U. Coll., London, England), J. D. A. Delhanty and H. P. Baden. *Ann Hum Genet* 35(2):149-160, 1971.

Data on unscheduled DNA synthesis and SV40 transformation of cultured cells are presented for three cases of xeroderma pigmentosum. Fibroblast cell cultures were obtained from a 33-year-old female and from two brothers aged seven and nine; control samples were taken from healthy subjects of the same sex and age group. The cultures were subjected to UV light at wavelength 2537 Å for 40 sec. Tritiated thymidine was then added to the cell cultures. Autoradiography of exposed cells showed labeled chromatin in 36% of the control cells and 2% of the xeroderma cells. Liquid scintillation spectrometry indicated that no repair synthesis was occurring in fibroblasts from the female xeroderma patient. Only low levels of repair were being carried out in cells of the two brothers. Further testing was done by subjecting xeroderma fibroblasts to 8-methoxypsoralen (8-MOP) and/or long wave UV. It was found that neither treatment alone produced any effect; but when both treatments were given to the cells, scheduled DNA synthesis was inhibited and unscheduled DNA synthesis was non-existent. In normal fibroblasts, unscheduled DNA synthesis was detected following the treatment. When xeroderma cell lines were exposed to SV40 virus, no

increased susceptibility to infection was noted, and all lines demonstrated normal repair. Chromosomal analysis indicated that an increase in aberrations was found after low UV doses in all three patients, but the effect was more marked in the female. It is concluded that cell death in xeroderma pigmentosum cultures must result directly or indirectly from the presence of unexcised thymine dimers, since there is little if any incorporation of tritiated thymidine into fibroblasts of the female and only low incorporation of tritiated thymidine in the two brothers. The fact, however, that there are varying degrees of xeroderma pigmentosum indicates that genetic heterogeneity is a feature in the disease.

- 1032 A COMMON BIOCHEMICAL CHANGE IN SV40 AND POLYOMA VIRUS: TRANSFORMED MOUSE CELLS COUPLED TO CONTROL OF CELL GROWTH IN CULTURE. (E.) Mora, P. T. (Natl. Inst. Neur. Dis. Stroke, Natl. Inst. Hlth., Bethesda, Md.), F. A. Cumar and R. Brady. *Virology* 46(1):60-72, 1971.

An investigation is presented which deals with enzyme depression in virally infected permissive cells, biochemical changes in transformed cells, and enzyme activity in cocultivation of transformed and nonvirally transformed cells. Cell lines, cloned derivatives from a single cell, from mouse embryos were used as well as 3T3 cells. Loss of specific activity of amino sugar transferase did not occur after productive infection by polyoma virus in the two lines studied. The effect of the virus in altering the growth properties of the cells and the biosynthesis of the higher gangliosides appear to be closely coupled. In polyoma and SV40 virus transformed cell lines, the higher gangliosides were greatly reduced, concomitant with the reduction of the activity of the hematoside N-acetylgalactosaminyltransferase. Changes in the amino sugar transferase activity paralleled the changes in phenotypic growth properties in cultures of both polyoma and SV40 virus-transformed cells and in the flat derivatives of these lines where there was a trend toward reversion to levels in uninfected cells. In cocultivation experiments no evidence of a factor influencing enzyme activity was detected in either the enzymatically active or inactive cells. Enzyme inhibitor was not detectable in the homogenate or in subcellular fractions of the virally transformed cells. It is assumed that the control of enzyme activity occurs at the protein biosynthesis level. The repressor-like mechanism in SV40 and polyoma virus induced cell transformation is paralleled by the biochemical findings.

- 1033 POLYOMA VIRUS PROTEINS: I. MULTIPLE VIRION COMPONENTS. (E.) Roblin, R. (Salk Inst., San Diego, Calif.), E. Hårle and R. Dulbecco. *Virology* 45(3):555-566, 1971.

Characterization of polyoma virus-specific proteins is reviewed. A reexamination of purified polyoma virus preparations, separated by electrophoresis on sodium dodecyl sulfate (SDS)-polyacrylamide gels, showed at least six different polypeptide components which were not aggregates. These components were found to have



1034-1039)

molecular weights ranging from 15,000 to 86,000. The material used in most of the experiments was a single virus pool prepared by infection of primary baby mouse kidney cell cultures. The sum of the molecular weights of the virion polypeptides nearly equals or exceeds the estimated coding capacity of the viral DNA. The major capsid protein was found to be P2 containing 50-70% of radioactive arginine or lysine (its molecular wt = 48,000). Polyoma virions contain three small polypeptide components which are associated with viral DNA and might be host cell histones. The role played by minor polypeptide components in polyoma virus infection, transformation, and virus particle assembly is discussed.

- 1034 EPIITHELIOMESENCHYMAL INTERACTIONS IN THE PROLIFERATIVE RESPONSE EVOKED BY POLYOMA VIRUS IN ODONTOGENIC EPITHELIUM *IN VITRO*. (E.) Main, J. H. P. (Fac. Dent., U. Toronto, Ontario, Canada) and W. A. Waheed. *J Nat Cancer Inst* 47(3): 711-719, 1971.

Results of culturing odontogenic mesenchyme infected with polyoma virus (PV) for four wk, followed by the addition of fresh odontogenic epithelium, and results of culturing epithelium and mesenchyme of odontogenic origin with or without PV, are reported. Odontogenic tissues were taken from incisor tooth germs of 13 or 14 day C3H/He mouse embryos. PV-infected whole tooth bud cultures remained essentially unchanged until 24 days, when epithelium proliferated markedly; squamous metaplasia was marked in most proliferating cultures. Epithelial proliferation continued up to 62 days of *in vitro* growth. Transplants of proliferating cultures did not result in the development of a neoplasm at the site of transfer. Uninfected tooth germs did not show epithelial proliferation. Odontogenic epithelium, cultured alone, with or without PV, did not remain viable for more than ten days. Dental mesenchyme grown without PV, remained viable for more than 40 days. Mesenchymal cells infected with PV sometimes remained in small cohesive clumps for up to 32 days. Immediate recombination cultures of trypsin-separated dental epithelium and mesenchyme were made to show that such separation and recombination permitted subsequent morphological differentiation. In immediate recombination cultures of uninfected epithelium and mesenchyme, morpho-differentiation was seen by four days *in vitro*. When epithelium or whole tooth germs were added to mesenchyme grown for 28 days with PV, epithelium proliferated after ten days. The necessity of epitheliomesenchymal interactions for the development of the proliferative response to PV in mouse odontogenic tissues is suggested.

- 1035 FELINE LEUKEMIA-VIRUS INFECTION OF KITTENS: MORTALITY ASSOCIATED WITH ATROPHY OF THE THYMUS AND LYMPHOID DEPLETION. (E.) Anderson, L. J. (Animal Leukemia Res. Unit., U. Glasgow, Scotland), W. F. H. Jarrett, O. Jarrett and H. M. Laird. *J Nat Cancer Inst* 47(4):807-817, 1971.

- 1036 EXTRACTION OF ADENOVIRUS TYPE 5-INDUCED NUCLEAR CRYSTALLINE INCLUSIONS IN KB CELLS. (Fr.) Torpier, G. (Pasteur Inst., Lille, France) and P. A. Boulanger. *Ann Inst Pasteur Lille* 22:269-282, 1971.

- 1037 INDUCTION OF RESISTANCE TO EHRlich TUMORAL GRAFTS WITH THE AID OF VIRUSES CULTIVATED "IN VIVO" IN HOMOLOGOUS TUMOUR: PRELIMINARY NOTE. (E.) Nastac, E. (No affiliation), D. Alexandrescu, M. Hozoc and M. Stoian. *Rev Roum Inframicrobiol* 8(2): 83-89, 1971.

- 1038 MORPHOGENESIS OF RABBIT FIBROMA VIRUS: CORRELATION WITH PATHOGENESIS OF THE SKIN LESION. (E.) Prose, P. H. (New York U. Sch. Med., N.Y.), A. E. Friedman-Kien and J. Vilcek. *Amer J Path* 64(3):467-482, 1971.

- 1039 SV40 NEUTRALIZING ANTIBODIES IN SERA OF US RESIDENTS WITHOUT HISTORY OF POLIO IMMUNIZATION. (E.) Shah, K. V. (Sch. Hyg. Pub. Hlth., Johns Hopkins U., Baltimore, Md.), H. L. Ozer, H. S. Pond, L. D. Palma and G. P. Murphy. *Nature* 231(5303): 448-449, 1971.

See also:

- \* (Rev): 0906, 0909, 0913
- \* (Phys): 0994
- \* (Immun): 1042, 1043, 1044, 1045, 1046, 1047, 1051, 1054, 1057, 1062, 1065, 1070, 1073

- 1040 IMMUNOCHEMICAL RESEMBLANCE BETWEEN HUMAN LEUKEMIA AND HEN EGG-WHITE LYSOZYME AND THEIR REDUCED CARBOXYMETHYL DERIVATIVES. (E.) Arnheim, N. (Dept. Biochem., State U. New York, Stony Brook), J. Sobel and R. Canfield. *J Molec Biol* 61(1):237-250, 1971.

An investigation dealing with the failure of sensitive immunological techniques to detect common antigenic determinants is presented. Hen egg-white (HEL) and human leukemia lysozymes (HLL) were examined by radio-immunoassay, micro-complement fixation, and immuno-diffusion techniques. A general lack of cross-reactivity between native HLL and HEL was encountered even though the proteins had a similar structure. There was an immunological resemblance, however, between reduced carboxymethyl-human leukemia lysozyme (RCM-HLL) and RCM-HEL in their cross-reaction with antisera prepared against the denatured lysozyme. The results demonstrated that two proteins which appeared to have essentially no immunological resemblance using antisera directed against their native structures, could be found to have considerable antigenic similarity when antibodies directed against the denatured molecules were used. It was demonstrated that a cross-reaction between two protein derivatives was not due to antibodies directed against the modifying agent itself; anti-RCM-HLL cross-reacted with performic acid-oxidized HEL as well as with RCM-HEL and no cross reaction was found between the anti-RCM-lysozymes and RCM- or performic acid-oxidized derivatives of non-lysozyme proteins.

- 1041 THYMIDINE KINETICS IN HUMAN LYMPHOCYTE TRANSFORMATION: DETERMINATION OF OPTIMAL LABELING CONDITIONS. (E.) Sample, W. F. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and P. B. Chretien. *Clin Exp Immunol* 9(3):419-427, 1971.

The development of a method for determining the optimal concentration of exogenous thymidine and duration of exposure for incorporation studies in human peripheral lymphocytes is described. Tritiated thymidine was used as the DNA precursor and the kinetics of incorporation were studied during maximal PHA stimulation. With short pulses (one to four hr) the amount of label incorporated increased linearly with increasing concentrations of thymidine up to  $0.5 \times 10^{-4}M$ , which was optimal. Optimal labeling conditions could not be maintained for more than four hr with continuous exposure to a single pulse of ( $^3H$ )-thymidine. High concentrations of exogenous thymidine were required to attain flooding conditions (24.2  $\mu g/ml$  of culture). A failure to maintain optimal incorporation for long exposure periods was due in part to difficulty in maintaining saturating concentrations of thymidine and to degradation of precursor to products not incorporated into DNA.

- 1042 CYTOSTATIC ANTIBODY AND SV40 TUMOUR IMMUNITY IN HAMSTERS. (E.) Ambrose, K. R. (Oak Ridge Natl. Lab., Tenn.), N. G. Anderson and J. H. Coggin, Jr. *Nature* 233(5318):321-324, 1971.

The mechanism of the failure of the immune response

was investigated in newborn LVG/LAK Syrian golden hamsters injected sub-scapularly with a suspension of SV40 virus. The first series of experiments was conducted to detect the circulating antibodies index. Implanted diffusion chambers, which allow quantitative measurement of tumor growth and which are permeable to antibodies but not to cells, were placed for five days in weaned hamsters. It was found that during the first ten wk period, there was a large growth of circulating antibody, followed by a precipitous decline; the loss of antibody always preceded tumor formation. This observed transient occurrence of circulating antibody implies that the corresponding antigen is functional. Next, immunofluorescence studies were conducted. It was determined that infected and presumably transformed cells persist in fairly large numbers during the latent period and produce the antigen or antigens giving rise to circulating antibodies. SV40 target cells were incubated in sera from normal immunized hamsters and from animals with tumors, and then inoculated into implanted diffusion chambers. Normal serum gave a typical cell increase over five days, whereas the animals in the group receiving serum from the SV40 tumor-immune hamsters showed cytostasis which was comparable with that observed in chambers implanted in immunized donors. It was found that animals immunized to irradiated tumor cells and virus were resistant to SV40 tumor challenge, and that surgical removal of tumors caused an elevation in levels of circulating antibodies. The time course for tumor induction can be divided into four phases: 1) initial oncogenicity whereby the cells grow rapidly for a short period before an immune response occurs; 2) cytostatic immunity resulting in a period of very slow growth; 3) transition to local antigen excess; and 4) uncontrolled growth. If the SV40 model is valid for immunologic reactivity to autochthonous tumors in man, then the possibility of detecting cancer in the period of cytostatic antibody control exists.

- 1043 SPONTANEOUS OCCURRENCE OF PRECIPITATING ANTIBODIES TO THE MAMMARY TUMOR VIRUS IN MICE. (E.) Muller, M. (Med. Acad. "Carl Gustav Carus", Dresden, Germany), P. C. Hageman and J. H. Daams. *J Nat Cancer Inst* 47(4):801-805, 1971.

Spontaneously occurring antibodies are reported in C3Hf and GR mice prenatally infected with Bittner mammary tumor virus (MTV-S) or GR virus (MTV-P), resp. The findings are at odds with previous reports that these mouse strains are tolerant to the MTV strains which they harbor. Multiparous female mice and sometimes mice stimulated by hypophysis grafting, with or without primary autochthonous mammary tumors, were of the following strains: C3H/HeA, CBA/BIN, GR, GRf, (C57BL x CBA/BrA) $F_1$ , BALB/c/DeA and (C3H x O20) $F_1$  and (C3H x BALB/c) $F_1$ . Sera were tested in micro-Ouchterlony plates against purified MTV-S or MTV-P particles isolated from (C3H x O20) $F_1$  or GR mammary tumors. Sera reacted with intact B particles and with ether-treated MTV-S, but never with nucleoid preparations of the virus. This suggested that the reaction was due to a virus-membrane antigen. Since most sera precipitating MTV-S also precipitated MTV-P, it was



ht that both viruses had this membrane antigen. Binding of spontaneous antibodies precipitating and MTV-P in GR and C3Hf mice was noteworthy, it had not previously been possible to detect antibodies in these strains. It was shown that tolerance exists to the outer membrane antigen in mice infected either neonatally (C3H and CBA) or neonatally (GR and C3Hf).

ALTERATIONS OF FORSSMAN-ANTIGENIC REACTIVITY AND OF MONOSACCHARIDE COMPOSITION IN PLASMA MEMBRANE FROM POLYOMA-TRANSFORMED HAMSTER CELLS. (E.) Ka, A. (Massachusetts Gen. Hosp., Boston) and Y. Ka. *Biochim Biophys Acta* 241:403-411, 1971.

Investigation of the Forssman antigenic reactivity of the plasma membrane isolated from untransformed polyoma virus-transformed baby hamster kidney fibroblasts (BHK) is reported. BHK cells and polyoma virus-transformed BHK cells (BHK-Py) were ruptured by pressure homogenizer and plasma membrane and endoplasmic reticulum fractions, free of ribosomes, were prepared. Most Forssman antigenic reactivity was found in plasma membranes of BHK-Py cells. Some reactivity was found in endoplasmic reticulum of BHK cells. When BHK microsomes were incubated with the BHK-Py supernatant, or when the BHK-Py microsome was incubated with the BHK supernatant, there was no difference in the Forssman reactivity from that in non-treated microsomes. Trypsin treatment converted the isolated plasma membrane of untransformed BHK cells to a state of reactivity. The Forssman reactivity thus obtained in untransformed BHK membrane was still less than that of untreated BHK-Py membrane. Trypsin treatment of Forssman-reactive BHK-Py membrane decreased reactivity seen in untreated cells. The contents of neutral and aminosugars were decreased in the plasma membrane of BHK-Py cells as compared with that of BHK membrane; exceptions were ribose and glucose.

TWO-COLOR IMMUNOFLUORESCENCE STUDIES ON EBV-DETERMINED ANTIGENS. (E.) Klein, G. (Inst. Tumour Biol., Karolinska Inst., Stockholm, Sweden), L. Gergely and G. Goldstein. *Clin Exp Immunol* 8(4):593-602, 1971.

Fluorescein isothiocyanate (FITC) and tetramethylrhodamine-isothiocyanate (TRITC) were used in three fluorescence tests designed to determine the relationship between the membrane antigen complex (MA) of the Epstein-Barr virus (EBV) and genetically determined isoenzymes of the HL-type. The EBV-carrying lymphoblastoid cell lines were established from Burkitt's lymphoma biopsy specimens and were maintained in stationary suspension cultures. The fluorescence tests were carried out when 30-60% of the cells expressed EBV-associated membrane antigen. First, the double membrane staining technique was done, whereby the same field, after exposure to FITC and TRITC, was photographed with both a red and a green fluorescence emission, and then photographed simultaneously. This test showed that the anti-HL-A and the anti-MA conjugates react with at least partly different areas of the cell. In the second type of fluorescence test, anti-MA reactive sera and conjugates characterized by

asymmetric cross-blocking activity were tested against each other. Preliminary results indicated a virtual absence of any blocking effect; but when serum was permitted to saturate the sites thoroughly, it was found that the two conjugates stain exactly the same spots and sectors of the cell surface, the M-type staining red and the K-type staining green. Thus, these M and K sites can be assumed to represent different antigenic subcomponents of the membrane-associated viral-envelope complex. Finally, a fluorescence study was done to determine the relationship between anti-MA and anti-viral capsid antigens (VCA). Results showed that VCA positive cells were approximately ten times less numerous than MA-positive cells, and that when the cells were MA-negative, the VCA was also negative. Therefore, these two sites are distinct with respect to specificity.

1046 BLOCKING OF DIRECT MEMBRANE IMMUNOFLUORESCENCE IN TITRATION OF MEMBRANE-REACTIVE ANTIBODIES ASSOCIATED WITH EPSTEIN-BARR VIRUS. (E.) Gunven, P. (Karolinska Inst., Stockholm, Sweden) and G. Klein. *J Nat Cancer Inst* 47(3):539-548, 1971.

Burkitt's lymphoma (BL), a disease associated with Epstein-Barr virus, produces cells with membrane antigens (MA) on the cell surface. In this study, BL cells were exposed to various sera, followed by exposure to fluorescein-isothiocyanate (FITC)-conjugated reference IgG. The Blocking Index (BI) was calculated by subtracting the percentage of membrane-stained cells in the serum exposed sample from the percentage in the sample exposed to conjugate alone and dividing the difference by the latter value. Membrane antigen expression, assessed by the frequency of positive cells, and differing conjugate concentrations did not significantly affect blocking activity in either undiluted or serially diluted sera. However, low-blocking sera gave slightly lower BI's with higher degrees of MA positivity among target cells. Test-evaluation observations were carried out by five persons, four of whom recorded similar values. An average decrease in blocking of 0.5 BI U was found when two-fold dilutions were used; in addition, a linear decrease was found within certain ranges. These two facts indicate that the extrapolated regression line should start at 0.4 or 0.5 and the titration curve should start with a BI of 0.6 or 0.7. In adapting this test to clinical use, titration should be carried out in parallel on the same occasion with five two-fold dilution steps each time. Readings should be done under code by the same observer throughout. Also, the unblocked reference sample, as well as the positive and negative blocking controls, should be read first.

1047 CORRELATION BETWEEN PRESENCE OF LEUKEMIA VIRUS IN CULTURED CELLS AND THEIR IMMUNOGENICITY IN A LEUKEMIA ISOTRANSPLANT SYSTEM. (E.) Tennant, J. R. (Sloan-Kettering Inst., New York, N. Y.), G. Lamber-tenghi, S. Kingsley and E. de Harven. *J Nat Cancer Inst* 47(4):781-788, 1971.

Established cell lines of BALB/c thymus tissue, minced normal BALB/c embryos, C3H mouse connective tissue, normal Wistar rat embryo, Chinese hamster lung tissue, and human infant esophagus epithelium were exposed to

infection by the murine lympholeukemogenic virus, BALB/Tennant-leukemia (B/T-1). Each cell line had both infected and control cells, of which transfers were made at the fifth passage and thereafter at weekly intervals for injection into C57BR/cd female mice or for electron microscopy studies. Of the cell lines examined after contact with the B/T-1 virus, only the three mouse lines and the rat line became infected, producing numerous Type C particles and gaining specific immunogenicity; the cells of the BALB/c thymus tissue were markedly more immunogenic than the other three lines. Cells of the hamster line and cells of the human line, on the other hand, showed no evidence of viral infection. As for the C57BR/cd strain, pretreated mice and untreated controls were challenged with a standard dose of cells from an isografted leukemia which had originally been induced in the C57BR/cd host strain by the B/T-1 virus. No animal receiving the control fluid developed leukemia. However, all of those receiving the virus infected fluid plus a control line fluid died of leukemia at an early age, except for those receiving the BALB/c thymus tissue fluid. Only three-quarters of these latter mice died of leukemia, and then at an advanced age. Fluid derived from the hamster and human lines was not immunogenic in the isograft. The conclusions that can be drawn from the data are: a) certain established cell culture lines, but not all, will accept and produce the B/T-1 virus in large numbers; b) a specific immunogenicity, shared with cells of leukemias induced by the virus, is conferred to such cells by the virus; and c) presence of the virus in cells correlates well with their expression of the new, specific cellular immunogenicity. Immunogenicity was not found where the virus was not present.

- 1048 HL-A ANTIGENS IN CHRONIC MYELOID LEUKEMIA (CML) AND CHRONIC LYMPHOID LEUKEMIA (CLL). (E.) Degos, L. (Hosp. Saint-Louis, Paris, France), Y. Drolet, and J. Dausset. *Transplantation Proc* 3(3):1309-1314, 1971.

A study of the frequency of 26 HL-A antigens in two populations of patients, 47 with CML and 44 with CLL, was done. Two methods were employed, lymphocytotoxicity and platelet complement fixation, using 108 different alloantisera. The CML patients showed a higher frequency of HL-A3 and a lower frequency of HL-A12.

- 1049 SEROEPIDEMIOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA BY IMMUNOFLOUORESCENCE. (E.) Kawamura, A., Jr. (Inst. Med. Sci., U. Tokyo, Japan) K. Hamajima, A. Gotoh, M. Murata, M. Takada, T. Sanpe, T. Takahashi, T.O. Yoshida, Y. Ito, T. Hirayama, K. Nishioka, T. Tachibana, C.-S. Yang, C.-H. Wang, S.-W. Ho, C.-T. Chu, H.-C. Chen, M.-M. Hsu, T.-C. Lynn, S.-M. Tu, T.-M. Lin and C.-H. Liu. *Gann* 10:185-198, 1971.

An extensive study on seroepidemiology of nasopharyngeal carcinoma in Japan and in Taiwan is presented. Burkitt lymphoma and nasopharyngeal carcinoma revealed strikingly different epidemiological pictures with regard to geographical distribution, race, sex, age, clinical manifestation, histopathological pictures,

and susceptibility to chemotherapeutics. A significantly higher incidence of positivity in anti-herpes-type virus antibody titer was observed in normal Taiwanese Chinese than in Japanese subjects; the morbidity rate of nasopharyngeal carcinoma in Taiwan is more than 100 times that in Japan. The sera from patients with either disease entity exhibit a very high and specific reaction with the acetone-fixed cultured Burkitt lymphoma cells carrying herpes-type virus when tested by the indirect fluorescent antibody method, indicating a highly specific relationship between them. Anti-herpes-titers higher than 1:640 dilution were 66.5% to 73.3% in Burkitt lymphoma and nasopharyngeal carcinoma patients respectively, whereas only 20% of these high titers were found in other neoplastic diseases. The rate of positive incidence in infectious mononucleosis was 42.8% and in malignant lymphoma 43.6%. The question is raised whether the herpes-type virus is an oncogenic agent or a mere passenger virus harbored in the lymphoid cells.

- 1050 SPECIFIC LYMPHOCYTE SENSITIZATION IN CANCER: IS THERE A COMMON ANTIGEN IN HUMAN MALIGNANT NEOPLASIA? (E.) Caspary, E. A. (Newcastle General Hosp., Newcastle upon Tyne, England) and E. J. Field. *Brit Med J* 2(5762):613-617, 1971.

The extraction of encephalitogenic factor (or antigenically similar material) (E.F.) from malignant tumor tissue is described and its antigenicity is compared with the basic protein extractable from human brain. This comparison was made in patients with malignant neoplasia as well as in those suffering from organic destruction of the nervous system. The material for brain extractable protein was taken postmortem from fatally injured patients without gross brain damage. Results revealed that an E.F.-like antigen is present in tumor tissue to which lymphocytes appear to become sensitized. It is a significantly better antigen in the cancer test than brain E.F. Basic protein derived from human brain, however, is a more effective antigen when lymphocytes from patients with destructive disease of the nervous system are tested. The results suggest that a common antigen may be present in human malignant growths, an antigen which manifests itself by specific lymphocyte sensitization.

- 1051 SURFACE ANTIGEN IN HERPES-TYPE VIRUS-CARRYING CELL LINES: AN IMMUNOFERRITIN STUDY. (E.) Sugawara, K. (Hokkaido U. Sch. Med., Japan) and T. Osato. *Gann* 10:257-263, 1971.

An investigation of the nature of the surface antigen in herpes-type virus-carrying cell lines by immunoferritin technique is presented. The immunoferritin study was carried out using two human cell lines, one (P3HR-1) was derived from a Burkitt line and the other (THE-3) from human embryo cell culture transformed by exposure to human leukemic culture fluid. Both types of cells were immersed in serum from a patient with nasopharyngeal carcinoma, which was immunofluorescence-positive to both cell lines, followed by treatment with ferritin-conjugated anti-human  $\gamma$ G rabbit antibody. A heavy ferritin reaction was observed on the surface membranes. Evidence that cells containing the virus particles were consistently positive for the specific



ritin tag of the surface membranes was established with the P3HR-1 line. This indicated a direct relationship between the synthesis of the surface antigen and infection with the herpes-virus. An antigenic similarity between the altered surface and the viral envelope suggested. It is conceivable that the envelopment itself may be responsible for sharing common antigenicity of the altered surface membranes with the virus particles.

52 IMMUNOCYTOLOGICAL STUDIES ON CULTURED CELLS DERIVED FROM NASOPHARYNGEAL CARCINOMA AND BURKITT LYMPHOMA, AND AN IMPROVED METHOD FOR IMMUNE ADHERENCE REACTION. (E.) Nishioka, K. (Aichi Cancer Res. Inst., Tokyo, Japan), T. Tachibana, T. Senne, M. Inoue, T. Hirayama, H. Sugano, T. O. Yoshida, Takada, A. Kawamura, Jr. and C.-H. Wang. *Gann* 10: 5-281, 1971.

Studies are presented which deal with the difference between the cultured cells from Burkitt lymphoma and nasopharyngeal carcinoma. Adherence of EA(IgM)C43 to nasopharyngeal carcinoma cells but not to Burkitt lymphoma cells was observed; adherence of EA(IgG) was negative to the nasopharyngeal cells and positive to Burkitt lymphoma. The effect of treatment with trypsin, phenol or acetone was evaluated by means of the percentage of cells forming rosettes with EA(IgM)C43 or with EA(IgG); the reactivity of nasopharyngeal cells was completely abolished with the former. No inhibition was observed with EDTA or with normal rabbit IgG. With the Burkitt lymphoma cells, acetone and phenol abolished reactivity of EA(IgG) and trypsin, EDTA and normal rabbit IgG showed no effect. It is suggested that the interaction of Burkitt lymphoma with EA(IgG) fits into the category of hemadsorption after viral infection. Similarity to early stages of simplex virus infection is observed. An improved method of immune adherence employing dithiothreitol as a stabilizing agent of positive pattern in the detection of extremely small amounts of antibody is described. Twenty minutes after the reaction of antigen-antibody and complement, 15 mM dithiothreitol was added followed by addition of human erythrocytes. This method completely prevents the conversion of positive immune adherence reaction into a negative pattern.

53 HL-A ANTIGENS IN HODGKIN'S DISEASE. (E.) Thorsby, E. (U. Hosp., Oslo, Norway), J. Falk, A. Engesth, and D. Osoba. *Transplantation Proc* 3(3):1279-1281, 1971.

A study of HL-A antigens in Canadian and Norwegian Hodgkin's disease patients is reported. Subjects studied included 78 Canadian and 39 Norwegian patients. The Canadian patients showed a significant increase of HL-A5 antigen compared to controls; 24% of Canadian patients and 9.2% of Canadian controls showed HL-A5 antigen. The increase in HL-A5 in Norwegian patients did not reach the 5% level of significance. No significant deviations from normal were found for HL-A antigens 4C\*(W5) or CM in Hodgkin's disease patients.

1054 INHIBITION OF ADENOVIRUS TYPE 2 BY HUMAN AND MONKEY INTERFERON. (E.) Henry, C. J. (Allegheny Gen. Hosp., Pittsburgh, Pa.) and M. Slifkin. *Proc Soc Exp Biol Med* 137(4):1432-1436, 1971.

A study performed to determine the extent to which monkey and human interferon inhibit adenovirus type 2 (Ad 2) growth in Vero monkey cells and in human embryonic fibroblasts is reported. Monkey interferon is more effective in inhibiting Ad 2 antigen synthesis and virion formation than is human interferon. The effect of a single dose of interferon on the growth of Ad 2 was determined; Vero cells and human embryonic kidney cells were treated with either monkey or human interferon, resp. Cultures were subsequently infected with Ad 2, and the effect of the two interferons on Ad 2 replication was observed. Monkey interferon reduced Ad 2 growth in Vero cells by about 95% at 90 hr postinfection; human interferon reduced infectious virus growth by 50-60% at 70 hr postinfection in human cells. Interferon inhibition of Ad 2 capsid antigen formation in human and monkey cells was also investigated. Monkey interferon inhibited Ad 2 antigen formation by 96-98% in Vero cells, while human interferon inhibited Ad 2 antigen formation by 65-80% in human embryonic kidney cells. Both monkey and human interferon reduced the number of cells showing positive fluorescence in homologous cell cultures. Results suggested that some serotypes of human adenoviruses were sensitive to interferon from animals other than their natural hosts.

1055 STUDIES ON THE NATURE OF ACQUIRED IMMUNITY AGAINST LEUKEMIA IN GUINEA PIGS. (E.) Gross, L. (VA Hosp., Bronx, N. Y.). *Acta Haemat* 45:218-231, 1971.

Experiments dealing with the induction of active immunity in guinea pigs by i.d. inoculation of leukemic cell suspensions are described. Leukemic cell suspensions of  $10^{-2}$  to  $10^{-8}$  concentration were inoculated under the skin of 3-6-wk-old "strain 2" of F<sub>1</sub> hybrid guinea pigs. In two experiments with s.c. inoculation of leukemic cells, 84 animals were treated; 53 of 55 "strain 2" guinea pigs given s.c. inoculation in one series developed leukemic cell infiltrations at the inoculation site; infiltration progressed to fatal stem-cell leukemia. In a related experiment, 0.1 ml doses of leukemic cell suspensions, varying in concentration from  $10^{-3}$  to  $10^{-7}$ , were inoculated i.d. into "strain 2" or F<sub>1</sub> hybrid guinea pigs. In two experiments, in which 96 animals were inoculated i.d., 67 developed i.d. tumors; 34 of these tumors regressed spontaneously. There was no apparent sex difference in the incidence of spontaneous regression of i.d. tumors induced in the inoculated animals. Twenty-one female guinea pigs and 11 males in which i.d. tumors regressed were reinoculated s.c. with leukemic cell suspension. Nineteen of the 21 reinoculated females and seven of 11 males resisted the challenging inoculation; induced immunity was apparently more pronounced in females than in males. Attempts were made to transfer the immunity developing in guinea pigs with regressed



i.d. tumors by serum of the immunized animals. This serum had no apparent neutralizing effect on the leukemogenic potency of leukemic cells.

- 1056 TISSUE ISOANTIGENS A, B, AND H IN CARCINOMA OF THE PANCREAS. (E.) Davidsohn, I. (Mount Sinai Hosp. Med. Ctr., Chicago, Ill.), L. Y. Ni and R. Stejskal. *Cancer Res* 31:1244-1250, 1971.

The effect of cancerous transformation on tissue isoantigens A, B and H of red blood cells of Groups A, B and O are investigated in human pancreatic tissue. The mixed cell agglutinin reaction (MCAR) was used to demonstrate A and B antigens in paraffin sections of normal pancreas, primary carcinoma of the pancreas and metastatic carcinoma of the pancreas. Pancreatic tissues from 73 patients were examined; there were 19 biopsy specimens with no histological evidence of carcinoma. In all 19 normal samples, MCAR was positive (i.e., the three isoantigens were present). In 22 of 26 biopsies diagnosed as carcinomas, MCAR was negative. Eighty-four percent of metastatic carcinoma tissue samples were negative on MCAR, indicating loss of the three isoantigens or impairment of their demonstrability. In five of 54 primary carcinomas, MCAR was positive and in four primary carcinomas, MCAR was negative in some areas, positive in others. In pancreatic carcinomas, two morphologically distinct cell populations were present: small highly anaplastic cells, and less anaplastic signet-ring cells. Anaplastic small cells were MCAR-negative, while signet-ring cells were MCAR-positive. Furthermore, only MCAR-negative anaplastic cells were present in metastases. A possible technique for early diagnosis of carcinoma of the pancreas was discussed.

- 1057 MALIGNANT AND TRANSFORMING ACTIVITY OF ROUS SARCOMA VIRUS (RSV): III. DETECTION OF TUMOR-SPECIFIC TRANSPLANTATION AND MEMBRANE ANTIGENS IN MOUSE CELL LINES TRANSFORMED *IN VITRO* BY RSV. (E.) Kryukova, I. N. (Acad. Med. Sci., Moscow, U. S. S. R.), O. V. Babkova and I. B. Obukh. *J Nat Cancer Inst* 47(4):819-827, 1971.

Experiments designed to investigate immunogenicity and immunosensitivity of two Rous sarcoma virus (RSV)-transformed mouse embryo cell lines are described. Two Af mouse-embryo cell lines were used: N27, transformed by a Djadkova strain of RSV, and N30, transformed by an Af mouse variant of RSV. Both cell lines had lost tumor-producing activity in syngeneic hosts. In isograft rejection tests, Af mice pretreated with an injection of N27 or N30 cells were tested for resistance against cells of a Schmidt-Ruppin RSV-induced tumor. Tumors developed in all challenged mice. Tumors developing in mice pretreated with N30 cells weighed more than tumors developing in mice pretreated with N27 cells. In tests of the cytotoxic reaction of sensitized lymphoid cells with target cells *in vitro*, lymphocytes sensitized with Carr-Zilber RSV-induced tumor cells destroyed 80% of N27 cells but were inactive against N30 cells. It appeared that N27 contained stronger or more abundant tumor-specific transplantation antigen (TSTA) than N30. Indirect immunofluorescence confirmed that N27 was immunologically more respon-

sive than N30. Findings suggested that the loss of oncogenicity of transformed tissue cultures was attributable neither to synthesis in their cells of strong RSV-TSTA, nor to a membrane-specific antigen (MSA). A new membrane antigen was detected in the cell membranes of both N27 and N30 cells; the appearance of this antigen coincided with infection of the mouse embryo cells with RSV.

- 1058 SOLUBILIZATION OF IgM- $\kappa$  SPECIFIC SURFACE MATERIAL FROM BURKITT LYMPHOMA CELL LINES. (E.) Nadkarni, J. S. (Dept. Tumour Biol., Karolinska Inst., Stockholm, Sweden), S-E. Svehag, J. J. Nadkarni and G. Klein. *Immunology* 20(5):667-679, 1971.

In some Burkitt lymphoma cases, the reactivity of the living tumor cell membrane with anti-immunoglobulin reagents has indicated that molecules with IgM specificity accumulate in the cell membrane. To test this hypothesis, two reactive cell lines (NK<sub>10</sub> and NK<sub>53</sub>) and one non-reactive cell line (NK<sub>10d</sub>) were derived from two teenage male Burkitt lymphoma patients. Crude solubilized membrane preparations, gel filtered fractions, and papain II digested fractions were tested for blocking of direct membrane fluorescence between anti-IgM or anti- $\kappa$  chain sera and NK<sub>10</sub> or NK<sub>53</sub> target cells. Blocking indices were calculated by subtracting the percentage of membrane stained cells obtained after exposure to the test fraction mixed with the conjugate from the percentage of positive cells obtained with the conjugate alone and dividing the difference by the latter. It was found that crude membrane preparations, solubilized sephadexed crude preparations, and papain II-digested sephadexed fractions of both NK<sub>10a</sub> and NK<sub>53</sub> gave complete inhibition of both anti-IgM and the anti- $\kappa$  reactions; while NK<sub>10d</sub> preparations showed no blocking activity. Indirect hemagglutination tests confirmed these results. Electron microscopy studies of all three cell lines, however, revealed no significant differences in appearance, although small protein fragments were present. When the materials were subjected to polyacrylamide electrophoresis, a minor difference in electrophoretic mobility was noted in that NK<sub>10d</sub>-papain digest migrated toward the anodic region faster than NK<sub>53</sub> digest. Hemagglutination inhibition with Fc  $\mu$  fragments indicated that these fragments inhibited the anti-IgM reactivity of sheep erythrocytes coated with proteolytic products of two membrane reactive cell lines; however, Fab  $\mu$  fragments did not, possibly because the amounts used were too small. The present results indicate that it may be possible to solubilize and recover membrane-bound specific antigens from tumor cells in quantities sufficient for further biological and detailed chemical investigation.

- 1059 ANTIBODIES IN HUMAN AND MONKEY SERA TO HERPES TYPE VIRUS FROM A CHICKEN WITH MAREK'S DISEASE AND TO EB VIRUS DETECTED BY THE IMMUNOFLUORESCENCE TEST. (E.) Naito, M. (Res. Inst. Microbial Dis., Osaka U.), K. Ono, T. Doi, S. Kato and S. Tanabe. *Biken J* 14(2):161-166, 1971.

Sera of 144 subjects, 72 of whom worked in direct contact with chickens and 72 of whom were office wor-



rs with little contact with chickens, were tested for detection of antibody activities to herpes type virus (HTV) (Biken C strain) and to Epstein-Barr (EBV) by the indirect immunofluorescent technique. Higher antibody titers to chick-HTV and EBV were found in the sera of the poultry workers. Sera from 48 cynomolgus monkeys used as controls showed little or no antibody to chick-HTV or EBV.

1060 HL-A AND HODGKIN'S DISEASE. (E.) Morris, P. J. (Royal Melbourne Hosp. Cancer Inst., Australia) and J. F. Forbes. *Transplantation Proc* (3):1275-1277, 1971.

A study of the frequency of HL-A antigens in 127 Australian patients with Hodgkin's disease is reported. Increased frequencies for 4 HL-A antigens were found: 4C, W5, HL-A11 and HL-A7. The percentages of Hodgkin's disease patients showing these respective antigens were: 37.0%, 32.3%, 28.6% and 8.6%. By comparison, the percentages of normals showing these respective antigens were: 26.0%, 2.2%, 13.5% and 25.2%. In 40 patients genotyped for HL-A there was a greater gametic association between HL-A2 and HL-A12 in Hodgkin's patients than in the normal Australian population.

1061 THE HL-A SYSTEM IN TROPHOBLASTIC NEOPLASIA. (E.) Lawler, S. D. (Royal Marsden Hosp. London, England), P. T. Klouda and K. D. Bagshawe. *Lancet* (7729):834-837, 1971.

The results of a study of the HL-A system in Caucasian patients with trophoblastic neoplasia are described. Fifty-three patients, 52 spouses, and 18 children were examined for reaction frequencies of the HL-A antigens. Subjects included 21 patients with choriocarcinoma following live-term birth, 20 husbands of choriocarcinoma patients, and 18 children from pregnancies antecedent to choriocarcinoma. HL-A incompatibility scores between husbands and choriocarcinoma patients did not differ significantly from scores in a series of normal subjects. Evidence for an interaction between the ABO and HL-A antigen systems was also sought. The influences exerted by the ABO and HL-A systems in choriocarcinoma appeared to be mutually independent.

1062 SEROLOGICAL STUDIES OF TUMOR ANTIGENS IN CHEMICAL- AND VIRUS-INDUCED THYMIC LYMPHOMAS. (E.) Doell, R. G. (Stanford U. Sch. Med., Calif.) and B. J. Mathieson. *Cancer Res* 31:1285-1289, 1971.

Tumor antigens on the cell surface of thymic lymphoma cells from chemical- and virus-induced lymphomas of C57BL mice and virus-induced tumors of Wistar-Kyoto rats have been studied with the use of immunofluorescence on viable cells with rat, rabbit, and monkey antisera. Cells from most lymphomas induced by chemicals or viruses were positive for cell surface antigen. The only tumors not consistently positive were C57LV-induced tumors tested against rat anti-radiation leukemia virus-induced antiserum. Thymuses from mice at early intervals after injection of C57LV were tested to determine at what time the

cell surface antigen was first detectable by immunofluorescence. Using rabbit or rat antiserum, a new cell surface antigen was detected at 48 hr post-injection. Rat antisera to virus-induced rat thymic lymphoma cells gave a precipitin line in Ouchterlony double diffusion analysis when tested with virus isolated from plasma of tumor-bearing rats or from mouse lymphoma extracts. This reaction is believed to be due to the group-specific (internal) antigen of the murine leukemia viruses, since ether treatment of the virus preparations was required to obtain it. The results suggest that both radiation and certain chemicals activate the same leukemogenic virus, supporting the hypothesis of a common mechanism of action of these treatments.

1063 TUMOR IMMUNITY IN HAMSTERS IMMUNIZED WITH FETAL TISSUES. (E.) Coggin, J. H., Jr., (Molecular Anat. Prog., Oak Ridge Natl. Lab., Tenn.), K. R. Ambrose, B. B. Bellomy and N. G. Anderson. *J Immun* 107(2):526-533, 1971.

Based on the principle that ontogeny repeats phylogeny applies at the molecular level and that early events of embryogenesis are morphologically similar in all vertebrates, tumor specific transplantation antigens were examined in different species. Adenovirus 31, when injected into neonates subcutaneously produced tumors in hamsters after 40-50 days. Immunization of four-week-old animals thus infected against tumorigenesis showed 40-50% protection with ten-day irradiated hamster fetal cells whereas with 14-day fetal tissue immunization was ineffective. Adult kidney immunization potentiated tumor development. A similar experiment revealed that nine-day fetal tissue induced about 28% protection with a better response in males. Females were protected against a low cell challenge level following immunization with ten-day fetal tissue (40% protection at 40 days), but males were completely protected when similarly immunized. In nature, only females are normally exposed to fetal antigens during pregnancy and their lower response to immunization may be the result of a maturational control mechanism with respect to the fetal homograft. Irradiated SV40 tumor cells conferred nearly absolute protection to SV40 tumor. Cytostatic (C) antibody invariably appeared when tumorigenesis was successfully interrupted and failed to appear when unirradiated fetal cells were used. It is suggested that the monitoring of C antibody may be useful in the detection of whether a tumor has been eradicated or recurs in man.

1064 ANTIBODIES PRODUCED BY IMMUNIZATION OF GOATS WITH 60S RIBOSOMAL SUBUNITS FROM NOVIKOFF HEPATOMA ASCITES CELLS (35812). (E.) Busch, H. (Baylor Coll. Med., Houston, Texas), R. K. Busch, W. H. Spohn, J. Wikman and Y. Daskal. *Proc Soc Exp Biol Med* 137(4):1470-1478, 1971.

60S ribosomal subunits, which contain 28S ribosomal RNA, were derived from polysomes of normal liver cells and cells infected with Novikoff hepatoma. These subunits were used as antigens to determine whether the same or different types of antibodies would be produced. Goats immunized with 60S ri-

bosomal subunits of Novikoff hepatoma ascites cells produced agglutinins for Novikoff hepatoma ascites cells. These antibodies agglutinated Walker 256 carcinosarcoma ascites cells as well, but did not agglutinate spleen white cells. Novikoff hepatoma ascites cells were also mildly positive with chicken and sheep antigen. However, goats immunized with 60S ribosomal subunits of normal liver did not produce agglutinins. It is believed that different antibodies are formed in response to immunization with tumor and normal liver 60S ribosomal subunits. Novikoff hepatoma ascites cells were also incubated with the antiserum to tumor 60S ribosomal subunits and then were subjected to fluorescein-labeled rabbit anti-goat  $\gamma$ -globulin; strong ring type fluorescence was exhibited. When this was repeated with normal liver 60S ribosomal subunits, fluorescence was much weaker. When the reaction of Novikoff hepatoma antiserum to Novikoff hepatoma ascites cells was observed, it was found that the growth of the tumor cells was markedly inhibited.

1065 STUDIES ON EB VIRUS IN ADENOID: I. ANTI-EB VIRUS TITER IN SERA FROM PATIENTS WITH ADENOID VEGETATION: II. DETECTION OF EB VIRAL ANTIGEN IN CULTURE CELL LINE FROM ADENOID TISSUES. (Jap.) Hosokawa, T. (Nagoya City U. Med. Sch., Japan). *J Nagoya U Med Ass* 22(1):172-196, 1971.

1066 A STATISTICAL ANALYSIS OF THE ADHERENCE OF ALLERGIZED LYMPH-NODE CELLS TO MOUSE BP8 TUMOUR CELLS *IN VITRO*. (E.) Callender, M. E. (Dept. Path., U. Cambridge, England) and B. V. Hall. *Brit J Exp Path* 52(2):209-213, 1971.

1067 THE INFLUENCE OF PRECEDING IMMUNIZATION WITH BCG ON THE GROWTH OF UVT TUMORS IN MICE. (Ger.) Wolf, M. (German Inst. Virus Res., Berlin) and C. Wolf. *Arch Geschwulstforsch* 37(3):210-212, 1971.

1068 ANERGY AND RECOVERY IN A CHILD WITH STAGE I HODGKIN'S DISEASE. (E.) Starling, K. A. (Baylor Coll. Med., Houston, Texas), M. A. South and D. J. Fernbach. *J Pediat* 79(4):666-668, 1971.

1069 ENHANCEMENT OF METASTASES BY L-ASPARAGINASE IN A MOUSE TUMOR SYSTEM. (E.) Deodhar, S. D. (Cleveland Clin. Fdn., O.). *J Reticuloendothel Soc* 10:212-222, 1971.

1070 IMMUNOLOGICAL RELATIONSHIPS BETWEEN CAPSID COMPONENTS OF ADENOVIRUSES OF DIFFERENT HOST CELL SPECIES ORIGIN. (E.) Norrby, E. (Karolinska Inst., Stockholm, Sweden), R. G. Marusyk and G. Wadell. *Canad J Microbiol* 17(9):1227-1237, 1971.

1071 IMMUNOHISTOLOGICAL STUDIES ON GASTRIC MUCOSAL GLYCOPROTEIN IN GASTRIC CARCINOMA. (E.) Kawasaki, H. (Kurume U. Sch. Med., Japan), K. Imasato and E. Kimoto. *Gann* 62(3):171-176, 1971.

1072 THE ELECTROPHORETIC MOBILITY OF BP8 ASCITES TUMOUR CELLS AND ALLERGIZED LYMPH-NODE CELLS AFTER TREATMENT WITH INFLAMMATORY MEDIATORS, PTOMAINES POLYAMINES, ANTISERA AND NEURAMINIDASE OR HEPARIN. (E.) Mitchell, D. M. (Dept. Path., U. Cambridge, England) and D. B. Cater. *Brit J Exp Path* 52(2):152-171, 1971.

1073 SERO-EPIDEMIOLOGICAL SURVEY ON YABA AND 1211 VIRUS INFECTIONS AMONG SEVERAL SPECIES OF MONKEYS. (E.) Tsuchiya, Y. (Natl. Inst. Hlth. Nakato, Japan) and I. Tagaya. *J Hyg* 69(3):445-451, 1971.

1074 TUMOR-SPECIFIC ANTIGEN SOLUBILIZED BY HYPER- TONIC POTASSIUM CHLORIDE. (E.) Meltzer, M. S. (Natl. Cancer Inst., Bethesda, Md.), E. J. Leonard, H. J. Rapp and T. Borsos. *J Nat Cancer Inst* 47(3):703-709, 1971.

1075 INFLUENCE OF EHRlich ASCITES CARCINOMA ON REPOPULATING ABILITY OF MOUSE BONE MARROW CELLS. (E.) Clerici, E. (Inst. Gen. Path., U. Milan, Italy), P. Mocarelli, M. L. Villa and N. Natale. *J Nat Cancer Inst* 47(3):555-560, 1971.

1076 SEARCH FOR ANTIBODIES AGAINST ASPERGILLUS FLAVUS ANTIGENS IN PATIENTS WITH PROLIFERATIVE DISEASES. (Pol.) Adamek, T. (Acad. Med., Krakow, Poland), J. Aleksandrowicz, Z. Laskownicka, A. Porebska and K. Zemburowa. *Pol Tyg Lek* 26(38):1470-1471, 1971.

1077 COMPARISON BETWEEN THE EFFECT OF RABBIT ANTI-RAT LYMPHOCYTE SERA RAISED BY THYMUS, THORACIC DUCT, AND SPLEEN LYMPHOCYTES ON SECOND-SET TUMOR ALLOGRAFT IN THE RAT. (E.) Girardet, R. E. (State U. New York Downstate Med. Ctr., Brooklyn), N. Glass, J. Patti and B. Gardner. *J Surg Res* 11(9):433-440, 1971.

1078 EPIDERMIOID CARCINOMA OF THE LIP AFTER RENAL TRANSPLANTATION: REPORT OF TWO CASES. (E.) Berger, H. (UCLA Sch. Med., Los Angeles, Calif.), R. Goldman, H. C. Gonick and J. Waisman. *Arch Intern Med* 128:609-612, 1971.

1079 ISOLATION AND CRYSTALLIZATION OF  $\alpha_1$ -FETOPROTEIN FROM A PRIMARY LIVER CELL CARCINOMA: II. COMMUNICATION. (Ger.) Lehmann, F. G. (Marburg/Lahn U. Clin., Germany) and D. Lehmann. *Z Klin Chem* 9(4):309-313, 1971.

1080 EFFECT OF THE "HOST-TRANSPLANT" REACTION ON THE TRANSPLANT IMMUNITY AGAINST HOMOLOGOUS TUMOR. (Rus.) Semenov, V. F. (Smolensk Med. Inst., U.S.S.R.) and A. S. Shevelev. *Vop Onkol* 17(6):69-74, 1971.



(1081-1083)

1081 RESISTANCE OF MICE TO EHRLICH ASCITES TUMOUR  
AFTER IMMUNISATION WITH LIVE *Salmonella*  
*enteritidis* 11RX. (E.) Hardy, D. (Dept. Microbiol.,  
U. Adelaide, South Australia) and I. Kotlarski. *Aust*  
*J Exp Biol Med Sci* 49(3):271-279, 1971.

1082 INTERACTION OF TRANSPLANTS OF THE EHRLICH  
CARCINOMA: LACK OF LOCAL REACTION TO SUB-  
CUTANEOUS TRANSPLANTS IN THE PRESENCE OF LATE INTRA-  
PERITONEAL TUMOUR. (E.) Hartveit, F. (Gade Inst., U.  
Bergen, Norway) and D. B. Cater. *Acta Path Microbiol*  
*Scand* 79:423-431, 1971.

1083 ENHANCED IMMUNE RESPONSE TO LEUKAEMIA. (E.)  
Haltermann, R. H. (Nat. Cancer Inst., Bethes-  
da, Md.) and B. G. Leventhal. *Lancet* 2(7726):  
704-705, 1971.

See also:

- \* (Rev): 0902, 0904, 0907, 0908, 0914, 0931
- \* (Viral): 1006, 1013, 1020, 1039

- 1084 CONTRIBUTION TO THE "CANCER AVEC CIRROSE" (HANOT) PROBLEM IN CHILDHOOD. (Ger). Griss, P. (Heidelberg U., Germany) and U. Schulz. *Acta Hepatosplen (Stuttgart)* 18(4):262-273, 1971.

The morphology of infantile hepatocarcinoma combined with cirrhosis is described on the basis of three autopsied cases. Primary tumors of the liver have an incidence of 0.2-5.8% of all malignant epithelial tumors occurring in childhood. Tumors occurring in the first two years of life are of embryonic origin (hepatoblastoma) and are characterized by morphologic peculiarities, while the morphology of primary tumors of the liver in later childhood resembles that of adult cancers of the liver, combined for the most part with cirrhosis. The three cirrhotic cancers described originate from 10-, 12- and 14-yr-old boys. The known occurrence of primary cancers of the liver in children up to the age of 16 comprised 273 cases, of which 37 were combined with cirrhosis of the liver; hepatoblastomas accounted for 53.2% of cases. Male children were afflicted twice as frequently as female children. Primary cancer of the liver in older children was a large-cell cancer compared to hepatoblastoma. The cells resembled normal liver epithelial cells, and contained an acidophilic cytoplasm, large nuclei with loose chromatin, and a distinct nucleolus. Typical was the multi-row trabecular arrangement of tumor cells and glycogen storage. Bile-producing ability could be impaired, pulmonary metastases were frequent, and cerebral and skeletal metastases were rare. Two of the cases described were trabecular hepatocellular cancers with reduced bile formation and pulmonary metastases; the third case was diagnosed as an anaplastic hepatocellular liver cancer. It is generally recognized that there exists a causal relationship between primary liver cancer and cirrhosis of the liver as diseases predisposing to cancer. Childhood cirrroses have a specific morphology and genesis, with giant cell hepatitis and morbus hemolyticus neonatorum playing a special role; in addition, virus hepatitis and serum hepatitis can cause childhood cirrroses. Among 37 childhood cancers with cirrhosis of the liver it was found that: 11 were Laennec's cirrhosis; five, postnecrotic Marchand's cirrhosis; four, biliary cirrhosis following morbus hemolyticus neonatorum; two, chronic hepatitis with cirrhosis; one, liver tuberculosis with cirrhosis; and 15 were unclassified. Prognosis was poor because the disease was diagnosed too late. Detection of  $\alpha$ -1-fetoglobulin in the serum of children was an indicator for early diagnosis of this tumor form.

- 1085 IRREVERSIBLE PRENEOPLASTIC DEFECT IN ALKALINE PHOSPHATASE IN CANCERIZATION OF TRANSITIONAL EPITHELIUM. (E.) Stiller, D. (Inst. Path., Friedrich-Schiller-U., Jena, Germany) and H. Rauscher. *Exp Path* 5:255-258, 1971.

Defective alkaline phosphatase activity in transitional epithelium of the urinary bladder is reported in rats injected s.c. with *n*-dibutyl nitrosamine. Rats were treated with 200 mg/kg of *n*-dibutyl nitrosamine at intervals of one wk. After 21 wk postinoculation, alkaline phosphatase disappeared in circumscribed areas of the bladder epithelium; loss of enzyme activity was followed by broadening of the

epithelial layer. By 27-35 wk, intense local epithelial proliferation occurred which later developed into papillomas. Alkaline phosphatase activity was absent from proliferating regions. Metastasizing carcinomas eventually developed in papillomatous areas. Cancer cells lacked alkaline phosphatase activity, although the enzyme was present in capillaries in the stroma of papillomas. Loss of alkaline phosphatase in areas undergoing *n*-dibutyl nitrosamine carcinogenesis was irreversible; enzyme-deficient areas persisted after the carcinogen was discontinued.

- 1086 HISTOGENESIS OF ODONTOGENIC TUMORS. (E.) Eversole, L. R. (U. Kentucky Coll. Dent., Lexington), C. F. Tomich and H. M. Cherrick. *Oral Surg* 32(4):569-581, 1971.

A new histogenic classification which correlates sequential changes in odontogenesis with tumor formation in the mixed group of odontogenic neoplasms is presented. It is based on the theory that tumors arise *de novo* at one particular stage of odontogenesis and do not progress or differentiate any further. This is supposedly because chemical "maturation factors" during normal odontogenesis cease to cause cellular differentiation beyond a particular stage. The new classification divides odontogenic tumors into categories. The simplest is the ameloblastic fibroma, which is composed mainly of primitive odontogenic epithelium suspended in an embryonal fibromyxomatous connective tissue; a variation of this tumor type has a basal lamina between the epithelial and mesenchymal layer. Other ameloblastic fibromas may involve mesenchymal maturation rather than differentiation, such as dense fibrous connective tissue in the mature variant and accumulation of histiocytes and dystrophic calcification in xanthomatous variants. The amelodontoblastoma would theoretically occur next. This tumor would be comprised of differentiated ameloblasts and odontoblasts occurring in the absence of either enamel or dentine matrix. Thirdly, the ameloblastic fibroma with dentinoid formation is considered. This tumor is incapable of inducing enameloid production, probably because of haphazard histomorphology. Lastly, the ameloblastic fibro-odontoma is listed. This tumor is comprised of all components encountered in the fully differentiated odontogenic apparatus, and it differs from an odontoma in that a preponderance of dental papilla-like tissue is present. A review of odontogenic histodifferentiation in embryogenesis is given, and the possibilities of ameloblastomatous, carcinomatous, and sarcomatous transformation are discussed.

- 1087 HISTOGENESIS OF ANAPLASTIC EPIDERMOID CARCINOMA AND STROMAL REACTION IN THE NASOPHARYNX. (E.) Chen, H.-C. (Coll. Med., Natl. Taiwan U., Taipei), S. Yeh and H. Sugano. *Gann* 10:215-233, 1971.

A comparative study on the cytogenesis of the individual component cancer cells from patients with nasopharyngeal carcinoma and normal nasopharyngeal tissue as observed under the electron microscope and light microscope is presented. Polyhedral basophilic can-



cells originated from the ciliated columnar or glandular epithelium and featured many free ribosomes, prominent Golgi complex, and the presence or absence of secretory granules. Large clear cancer cells were variants of these cells and were distinguished by their large vesicular nucleus containing one or two nucleoli. Secretory granules were present but tonofibrils were lacking. Cells arising from the squamous epithelium were of three types: typical basal cells with indented nuclei, absence of basement membrane, and occasional mitoses; spindle-shaped cells with fusiform nuclei, small spherical or irregularly shaped nucleolus, and coarse tonofibrils; and vesicular cells which were large, had a vesicular nuclear structure, coexisting tonofibrils, and secretory granules in the cytoplasm. Vesicular cells probably have bivalent potentialities for differentiation into squamous or columnar cells. Three basic types of stromal tissue are proposed for classification regardless of cellular type: one with no fibrous stroma discernible except for a very small amount of delicate connective tissue accompanying blood vessels and histological features such as syncytial strands and penetration of the tumor cell by lymphoid cell; another with loosely-textured connective tissue and conspicuous plasma cell infiltration; and a third with densely fibrous stroma and very few lymphoid cells. Some virus-like particles detected in a small proportion of cancer cells from three patients with nasopharyngeal cancer were morphologically similar to a member of the herpes-virus group.

88 THE MYOGENOUS ORIGIN OF GRANULAR MYOBLASTOMA. (Ger.) Tsakraklides, B. (Greek Red Cross Hosp., Athens) and N. X. Papacharalampous. *Zbl Pathol* 114(4):443-446, 1971.

Granular cell myoblastomas have hitherto been regarded as myoblastomatic derivatives, degenerative or regenerative manifestations of striated muscle fibers, tumors of neurogenic origin, or histiocytic proliferations with defective metabolism. The excision of a slowly-growing, painless, almond-sized swelling from the submandibular region of a 40-year-old woman, histologically diagnosed as a granular myoblastoma, revealed two previously undescribed histologic characteristics providing new information concerning the histogenesis of these tumors. Following removal, a new growth began developing, attaining the size of a tangerine after five years. It weighed 70 g, was of soft consistency, had a greyish-white color, and consisted of densely packed round or polymorphous cells which were 200  $\mu$  in diameter and arranged in bands. The cells contained fine-grained eosinophilic cytoplasm, with the cells having rod-shaped granules arranged in rows perpendicular to the longitudinal axis. Tissue taken from the periphery of the tumor contained crosswise striated muscle bundles or individual muscle fibers, some of which were degenerated and some well-preserved. The histologic structure was that of a typical granular myoblastoma. Previously unreported was the rod-like shape of the cytoplasmic granules in some cells and the crosswise striation of some cell elements which ripened into muscular cells. This last finding indicates that the elements are of myogenic origin. The

crosswise striation seems to result from the parallel arrangement of the rod-shaped granules and not from a degenerative process; this hypothesis is also supported by the existence of the nucleolus-containing nucleus.

1089 MORPHOLOGY AND MORPHOGENESIS OF ENDOTHELIAL HEMANGIOMA. (Rus.) Smol'yannikov, A. V. (Central Inst. Postgrad. Med., Moscow, U.S.S.R.) *Arch Pat* 33(6):14-21, 1971.

1090 PARAPHARYNGEAL MENINGIOMA WITH SPECIAL REFERENCE TO CELL OF ORIGIN. (E.) Shuangshoti, S. (U. Virginia Sch. Med., Charlottesville), M. G. Netsky and G. S. Fitz-Hugh. *Ann Otol* 80(3):464-473, 1971.

1091 MENINGIOMA OF THE PAROTID GLAND: AN INSIGHT INTO THE PATHOGENESIS OF EXTRACRANIAL MENINGIOMAS. (E.) Wolff, M. (Coll. Phys. Surg., Columbia U., New York, N.Y.) and R. M. Rankow. *Hum Path* 2(3):453-459, 1971.

1092 ALTERATION IN CELL PROLIFERATION IN MOUSE LUNG FOLLOWING URETHANE EXPOSURE: II. EFFECTS OF CHRONIC EXPOSURE IN TERMINAL BRONCHIOLAR EPITHELIUM. (E.) Kauffman, S. L. (State U. New York, Downstate Med. Ctr., Brooklyn). *Amer J Path* 64(3):531-540, 1971.

1093 VAGINAL ADENOCARCINOMA ARISING IN VAGINAL ADENOSIS. (E.) Ruffolo, E. H. (Tampa Gen. Hosp., Fla.), D. Foxworthy and J. C. Fletcher. *Amer J Obstet Gynec* 111(2):167-172, 1971.

See also:

- \* (Rev): 0925, 0926
- \* (Chem): 0956, 0970, 0980, 0993
- \* (Viral): 1038

- 1094 BURKITT'S LYMPHOMA: A TIME-SPACE CLUSTER OF CASES IN BWAMBA COUNTY OF UGANDA. (E.) Morrow, R. (Makerere Med. Sch., Kampala, Uganda), M. C. Pike, P. G. Smith, J. L. Ziegler and A. Kisuule. *Brit Med J* 2(5760):491-492, 1971.

Seven cases of Burkitt's lymphoma are reported from Bwamba County, Uganda, an isolated region in which most of the population practices subsistence farming, and in which malaria is hyperendemic. The seven cases (five males, two females) developed between October, 1966 and December, 1968; 5 of the cases developed between July-December, 1968. Patients were aged three to nine yr. Two patients were full sibs, living in the same house. No unusual happenings have been discovered between 1967-1968 to account for the cluster of cases. It is noted that this is the most discrete time-space cluster of Burkitt's lymphoma on record.

- 1095 CANCER OF THE COLON IN NIGERIANS AND AMERICAN NEGROES. (E.) Grillo, A. (U. College Hosp., Ibadan, Nigeria), L. F. Bond and W. W. Ebong. *J Nat Med Ass* 63(5):357-361, 1971.

The general pathological picture of carcinoma of the colon in Nigerian and American Negroes is compared in a study of 219 American Negroes and 85 Nigerians with this condition. Only in the age distribution of persons with colonic carcinoma and in the distribution of carcinomas within the colon did the Africans differ from the Americans. The youngest male American Negro with colon carcinoma was 18-yr-old, while the youngest Nigerian male was 11-yr-old. The youngest female American Negro with colon cancer was 44-yr-old, while the youngest Nigerian female was 22-yr-old. Of the subjects examined, 10% of American Negroes and 22-24% of Nigerians had carcinomas in the cecum; 24% of Americans and 48-54% of Nigerians had carcinomas in the anorectal area. The sigmoid area of the colon was affected in 29% of Americans and in 9% of Nigerians.

- 1096 LUNG CANCER IN JERSEY: ITS INCIDENCE AND ASSOCIATED BIOCHEMISTRY. (E.) Cragg, J. (Gen. Hosp., Jersey, Channel Isles). *Brit J Clin Pract* 25(8):360-365, 1971.

A study of 144 lung cancer patients in Jersey, Channel Isles, is detailed; Jersey, an area with virtually no industrial air pollution, has a high rate of incidence for lung cancer (1695 cases/million population in 1968 vs 1210 cases/million in England and Wales). There was no apparent concentration of lung cancer cases in any one area of Jersey, and lung cancer cases were equally spread throughout urban and rural areas of the island. Epidermoid cell lung carcinomas made up 40 cases; the undifferentiated type of carcinoma was seen in 41 cases (18 of these being oat cell tumors); there were seven cases of adenocarcinoma and 6 of "mixed" carcinoma. The male:female sex ratio in the epidermoid cancers was 39:1 and in undifferentiated cancers, 30:11. Most of the 113 lung cancer patients for whom smoking histories were available were heavy cigarette smokers. The average age for development of lung cancer was 63-yr-old for males and 62-yr-old for

females. Short diagnosis-death intervals (3.7 months) characterized oat cell lung carcinomas. Of 111 lung cancer patients whose electrolyte levels were estimated, 25 patients had low sodium levels, two had low sodium and potassium levels, and five had low potassium levels and normal sodium levels. Most low-sodium level patients had evidence of metastases. There was no clinical evidence of hypercalcemia in the lung cancer patients. There was one case of hyponatremic syndrome and three cases of gynecomastia.

- 1097 BIRTH CHARACTERISTICS AND LEUKEMIA IN CHILDHOOD. (E.) Fasal, E. (State Dept. Publ. Hlth., Berkeley, Calif.), E. W. Jackson and M. R. Klauber. *J Nat Cancer Inst* 47(3):501-509, 1971.

A case-control study, designed to investigate the association of birth wt, maternal age, birth order, sex, and social class with the risk of death from leukemia is reported. The cases examined consisted of 802 non-mongoloid, single-born children who died from leukemia in California at ages one to nine yr old between 1959 and 1965. No statistically significant association with leukemia mortality in children was found for maternal age or birth order. A summary excess risk of leukemia mortality of 60% was found for children with high birth wt. The association of high birth wt and leukemia mortality was significant for female children only; the summary excess risk for high birth wt children was about two-fold for females and only 1.2-fold for male children. In general, excess risk for high birth wt was greater for high maternal age. A significant association with leukemia mortality was also found for social class. The overall summary relative risk was one-third greater for children in the two highest social classes. Analysis by sex showed that this association was significant only in female children; the relative risk for children in higher social classes was 1.11 for males and 1.73 for females.

- 1098 AN EPIDEMIOLOGIC EVALUATION OF THE MORBIDITY AND DEATHS FROM MALIGNANT LYMPHOGRANULOMATOSIS IN THE YEARS 1961-1965. (E.) Gadomska, H. (Inst. Oncol., Warsaw, Poland) and Z. Karewicz. *Epidemiol Rev* 24(4):375-380, 1970.

Incidence and mortality figures for malignant lymphogranulomatosis in Poland for the years 1961-1965 are presented. During this period, 2566 new cases were recorded. An average of 64.9% of cases arose in males and 35.1% arose in females. The mean incidence rate in males was 2.2 cases/100,000 population and in females 1.1 cases/100,000 population. Among urban males the mean incidence rate was 2.3 cases/100,000 and in females 1.4 cases/100,000. The mean incidence rate among rural males was 1.9 cases/100,000 and in females 0.8 cases/100,000. The mean incidence rate of lymphogranulomatosis for males in five yr age groups shows a gradual increase; peaks in incidence occur in the 35-39-yr age group and in the 60-64-yr age group. A total of 1794 deaths from malignant lymphogranulomatosis occurred: 66.9% in males and 33.1% in females. The mean mortality rate in males was 1.6 deaths/100,



and in females 0.7 deaths/100,000. In towns this was 1.9 deaths/100,000 for males and 0.9 deaths/100,000 for females. In rural areas it was 1.6 deaths/100,000 for males and 0.7 deaths/100,000 for females.

STOCHASTIC ASSESSMENT OF LEUKEMIA INCIDENCE IN THE CITY OF KRAKOW AND IN THE KRAKOW REGION DURING THE YEARS 1951-1960. (Pol.) Bartkowiakowa, M. (Inst. Sci., Wroclaw, Poland) and K. Janicki. *Pol J Epidemiol* 26(40):1531-1533, 1971.

Results of a statistical study of leukemia incidence in the city of Krakow and in the Krakow region (including the city) are presented. The leukemia incidence can be approximately described by a Poisson distribution with intensity of leukemia incidence increasing linearly with time. The intensity of leukemia incidence, characterized by the formula " $a + b \cdot t$ " (where  $t$  is time) was analyzed and assessed for both years. Using the test of highest probabilities it is shown that coefficient " $a$ ", characterizing rate of increase of the leukemia incidence in consecutive years, is the same for both areas, whereas time-independent coefficient " $b$ " differs. These data, although incomplete, are similar to the world data characterizing the disease.

AN EPIDEMIC OF HODGKIN'S DISEASE? (E.) Heath, C. W. (Ctr. Dis. Control., H.S., Atlanta, Ga.), J. G. Rosenstock and G. L. *Lancet* 2(7721):426-427, 1971.

Hypothesis that Hodgkin's disease is transmitted from person to person by means of interpersonal contact is discussed in the light of a study of 34 patients with the disease in the Atlanta, Georgia, area. In interviews with patients or their near relatives, no instances of Hodgkin's disease occurring among patients' relatives came to light. In two instances were cases of Hodgkin's disease reported to have occurred in persons with whom patients came in contact. The same patients with Hodgkin's disease were examined for their distribution according to school attendance in the metropolitan area. Eleven patients who attended school in Atlanta attended 13 different high schools, with only one school being attended by more than one patient. Results indicated that Hodgkin's disease is not transmitted by the simple spread of an infectious agent but by interpersonal contact of affected persons.

FAECAL STEROID COMPOSITION AND ITS RELATIONSHIP TO CANCER OF THE LARGE BOWEL. (E.) M. J. (St. Mary's Hosp. Med. Sch., London, England) and V. C. Aries. *J Pathol* 104(2):129-139, 1971.

Results revealing substantial differences in the composition and composition of steroids and bile pigments in feces from four populations (England, Scotland, India and India) is reported. The English and Indians live on a normal Western mixed diet; the Ugandans live on a diet consisting largely of matoke (mashed banana). The urobilin concentration in feces of vegetarians (i.e., Indians and Ugandans) is much lower than that in feces from British

people. Thin-layer chromatography of fecal samples showed that the principal neutral steroids in all samples were coprostanol, cholesterol and coprostanone. There was a much greater concentration of neutral steroids in feces of English and Scottish subjects than in feces of Indians and Ugandans. In addition, neutral steroids were more highly microbially degraded in the former group than in the latter. The concentration of fecal acid steroids was more than 11 times greater in English and Scottish fecal samples than in samples from Indians and Ugandans. Acid steroids were also more highly microbially degraded in English and Scottish samples than in Ugandan and Indian samples. It was known that rates of cancer of the large bowel are markedly higher in England and Scotland than in Uganda and India. The results indicated that the concentration of degradation products of biliary compounds in feces varied between groups of people on different diets; if intestinal bacteria are able to produce carcinogens from such compounds, a possible mechanism relating diet and gut bacteria to cancer of the large bowel will have been established.

1102 INSULATION WORKERS IN BELFAST: 2. MORBIDITY IN MEN STILL AT WORK. (E.) Langlands, J. H. M. (Belfast City Hosp., Northern Ireland), W. F. M. Wallace and M. J. C. Simpson. *Brit J Industr Med* 28:217-225, 1971.

A survey of 252 asbestos insulation workers was undertaken to assess the effect of exposure to asbestos on the health of men currently engaged in insulation work. The proportion of male asbestos workers with abnormal chest X-rays increased with age and with number of yr worked in the industry. In men grouped according to their present ages, the average age of entering into the asbestos insulation industry was five yr younger in men with lung field abnormalities in their chest X-rays than in men with no such abnormalities. The frequency of chest X-ray abnormality, lung field or pleural, increased from 13% in men who had worked for less than ten yr in the industry to 85% in men who had worked for 30 yr or more. Pleural calcification was seen in 15 X-rays. Ten men had pleural fibrosis and lung field abnormality in addition to pleural calcification; these had worked for 25 yr or more as insulation workers. Five had pleural calcification with or without pleural fibrosis but no lung field abnormalities, and had worked for less than 25 yr. It was suggested that some young men in the series may have developed pleural calcification or fibrosis as a result of exposure in childhood to asbestos dust on the clothes of relatives working in the industry. Rales and clubbing, while uncommon in men whose X-rays showed only pleural abnormalities, were present in 61% and 11% resp. of men with lung field abnormalities. Men with pleural abnormalities alone had a mean single breath carbon monoxide transfer factor (Tl) similar to men with normal chest X-rays, but a lower mean forced expiratory volume in 1 sec. (FEV<sub>1.0</sub>)/forced vital capacity (FVC)%, and a lower peak flow rate (PFR). Men with lung field abnormalities had a significantly lower mean FVC and Tl than men with normal chest X-rays. Cigarette smoking among the insulation workers was associated with a greater impairment of lung function than was X-ray abnormality.

- 1103 INSULATION WORKERS IN BELFAST: 3. MORTALITY 1940-1966. (E.) Elmes, P. C. (Dept. Therap. Pharmacol., Queen's U., Belfast, Northern Ireland) and M. J. Simpson. *Brit J Industr Med* 28:226-236, 1971.

A study of the fate of all men known to have been employed since 1940 in insulation work in connection with the shipbuilding industry in Belfast is presented; insulation work entails chronic exposure to asbestos dust. The population examined comprised 170 men of whom 165 were available for follow-up; subjects ranged in age from less than 20-yr-old to more than 40-yr-old at time of entry into insulation work. Between 1940 and 1966, 98 of the 165 insulation workers died; the expected number of deaths in a comparable population is 37. Subjects were divided into four groups according to age at entry into insulation work; all four groups showed a high mortality beyond the age of 55-yr-old. At the time of the study, only five men had lived beyond 70-yr-old, and these five died at age 71- or 72-yr-old. Throughout the period the number of deaths observed among insulation workers exceeded the number of deaths expected; the increase was statistically significant during the period 1950-1955 and after. After 1950, cancer deaths among insulation workers were nearly eight times more frequent than expected. For the workers, deaths from larynx, lung or pleura cancers were 17 times more frequent than expected. The seven confirmed cases of mesothelioma in the insulation workers were in excess of the expected mesothelioma incidence. Mortality from cancer of the gastrointestinal tract and from fibrotic lung lesions was also especially high among insulation workers. The ratio of observed over expected deaths among workers was 2.6 for all causes, 3.9 for all cancers, and 17.6 for cancers of the lower respiratory tract and pleura. Comparisons within the group of insulation workers showed no correlation between age at first exposure to asbestos, or duration of exposure, and the excessive mortality. There were not enough known nonsmokers in the group to show any significant relationship between smoking and mortality.

- 1104 GROWTH DYNAMICS OF BEAGLE OSTEOSARCOMAS. (E.) Thurman, G. B. (U. Utah Coll. Med., Salt Lake City), C. W. Mays, G. N. Taylor, W. R. Christensen, C. E. Rehfeld and T. F. Dougherty. *Growth* 35(2):119-125, 1971.

Periodic radiographic examinations of beagles with osteosarcomas induced by internally deposited radionuclides are reported; the growth patterns of these tumors are described. Osteosarcomas were induced by i.v. injection of isotopes of radium, plutonium, thorium and strontium; 256 osteosarcomas were studied. Two groups of tumors were described: fast-growing tumors (tumor volume doubling time < 25 days); and slow-growing tumors (tumor volume doubling time > 25 days). Tumor volumes appeared to enlarge exponentially with time. Beagle osteosarcoma doubling times ranged from 4.7-60.3 days (average = 12.4 days). Growth rates of osteosarcomas appeared not to be significantly correlated with sex, administered radionuclide, injected  $\mu\text{C/kg}$ , tumor location, tumor calcification, tumor volume at autopsy, or age of animal at death.

- 1105 CELL KINETIC ANALYSIS OF A HUMAN MELANOMA *IN VITRO* AND *IN VIVO-VITRO*. (E.) Hagemann R.F. (Allegheny Gen. Hosp., Pittsburgh, Pa.) and L. M. Schiffer. *J Nat Cancer Inst* 47(3):519-525, 1971.

Both *in vitro* and *in vivo-vitro* studies were conducted on melanoma cells taken from a 45-yr-old female Caucasian in order to determine cell kinetic parameters. First, sternal bone marrow aspirates were obtained for the establishment of a viable melanoma cell line. Once this was accomplished, the following tests were run: the percent labeled mitosis method (after a 30 minute exposure to tritiated thymidine); the double-labeling method (after exposure to tritiated thymidine and carbon-14-labeled thymidine for 45 minutes each); and the continuous-labeling technique (after exposing the cells to tritiated thymidine every four hr). Then, *in vivo-vitro* studies were performed on two morphologically distinct populations of tumor cells; the double-labeling method was used. The values for cells growing *in vitro* (with the corresponding *in vivo-vitro* values given in parentheses) were as follows: labeling index=0.25 (0.23); DNA synthesis time ( $T_s$ )=14.5 hr (15.9 hr);  $G_2+0.7 M$ =5.3 hr;  $G_1$ =16.3 hr; cell-cycle time=36.1 hr (40 hr); and growth fraction=0.62 (0.58).  $T_s$  was determined in two other ways: cells growing in culture were double-labeled ( $T_s$ =15.6 hr); cells from a bone marrow aspirate were double-labeled *in vitro* ( $T_s$ =15.7 hr). Whereas small and large tumor cell populations could be distinguished, no significant parameter differences were noted. Thus, there was excellent correspondence between the cell-cycle parameters as measured *in vitro* and *in vivo-vitro*. It is felt that generalization from the data presented to other types of tumors, especially solid tumors, would at this time be extremely tenuous.

- 1106 COLONY GROWTH OF HUMAN LEUKEMIC PERIPHERAL BLOOD CELLS IN VITRO. (E.) Robinson, W. A. (U. Colorado Med. Ctr., Denver), J. E. Kurnick and B. L. Pike. *Blood* 38(4):500-508, 1971.

A study of the colony-forming potential of peripheral white blood cells (WBC) from patients with acute leukemia of all types on feeder layers of normal human WBC is reported. Peripheral WBC of 12 of 20 patients with acute granulocytic leukemia (AGL) formed more than 100 colonies/ $2 \times 10^5$  cells plated on normal WBC. The WBC of eight patients with AGL formed only small numbers of colonies (i.e., 0-37 colonies/ $2 \times 10^5$  cells plated). Cells from AGL patients with the highest peripheral blast cell counts generally gave rise to the greatest number of colonies on normal WBC feeder layers. Blood from four patients with acute lymphocytic leukemia and from three patients with acute stem cell leukemia did not yield significant numbers of colonies. When peripheral WBC from AGL patients were plated in increasing cell concentrations, there was a roughly linear relationship between number of nucleated WBC plated and number of colonies formed. Colonies formed from WBC of AGL patients appeared to go through a process of morphologic maturation to segmented granulocyte forms. It was found that leukemic WBC would not serve as feeder layers for leukemic cells.



07 DNA SYNTHESIS TIME IN LEUKAEMIC CELLS AS MEASURED BY THE DOUBLE LABELLING AND THE PERCENTAGE LABELLED MITOSIS METHODS. (E.) Harriss, B. (Clin. Res. Ctr., U. Ulm, Germany) and D. Hoelzer. *Cell Tissue Kinetics* 4:433-441, 1971.

The double labeling method of measuring the duration of the DNA synthesis phase in the cell cycle consists of exposing cells in the S-phase to an initial pulse of tritiated thymidine followed after an interval by a second pulse of carbon-14-labeled thymidine. The two labeled cell populations can then be recognized autoradiographically. This method was tested *in vivo* on a 66-yr-old man suffering from plasmacytoma. The first label was administered to the patient *in vivo* and the second label *in vitro*, with several values for the interval between the two labels. Results showed a mean estimate of  $19.8 \pm 3.4$  hr. Since the double labeling method has previously shown poor correlation with data derived from the labeled mitosis technique, a comparison of the two techniques was made. The labeled mitosis method yielded a DNA-synthesis duration of  $17.1 \pm 7$  hr. In further tests of both methods, cells of the inbred BDIX strain bearing acute leukemia were used. It was found that the percentage labeled mitosis technique gave a value of  $8.7 \pm 1.7$  hr. Again, the data correlated well, provided that choice in the autoradiographed population of the doubling exceeded 10 grains. It was concluded that the double labeling method is valid for the study of cell proliferation in leukemic blast cells.

1108 METASTATIC ADENOPATHIES IN MAMMARY GLAND CANCERS: STAGE OF OCCURRENCE. (Fr.) Le Gal, Y. (Med. Inst., Strasbourg, France) and J. P. Igot. *Ann Anat Path (Paris)* 16(1):9-25, 1971.

1109 THE MITOTIC INDEX IN BRONCHOGENIC CARCINOMA. (E.) Weiss, W. (Philadelphia Pulmonary Neoplasia Res. Proj., Pa.). *Amer Rev Resp Dis* 104(4): 536-543, 1971.

1110 THE FREQUENCY OF WARTS IN ATOPIC PATIENTS. (E.) Currie, J. M. (U. Oregon Med. Sch., Salem), R. C. Wright and O. G. Miller. *Cutis* 8(3): 243-246, 1971.

1111 ASBESTOS-RELATED CHEST DISEASE IN JOINERS. (E.) Fletcher, D. E. (North Lonsdale Hosp., Barrow in Furness, England). *Proc Roy Soc Med* 64(8): 837-838, 1971.

See also:

- \* (Rev): 0917
- \* (Immun): 1049

- 1112 RELATIONSHIP BETWEEN GLUCOSAMINE UPTAKE AND ALKALINE PHOSPHATASE IN HeLa CELLS: EFFECTS OF GLUCOSE AND PREDNISOLONE. (E.) Melnykovich, G. (VA Hosp., Kansas City, Mo.) and C. C. Costlow. *J Nat Cancer Inst* 47(3):527-534, 1971.

The relationship between glucosamine uptake and alkaline phosphatase levels was studied in two strains of HeLa cells. One strain, S3G, had a naturally low alkaline phosphatase level, while the other strain, S3K, had a relatively high level of this enzyme. The effect of the presence of glucosamine on cells grown in the presence of prednisolone, a glucocorticoid, was tested. It was found that, in most cases, prednisolone slightly decreased the total glucosamine incorporation, although uptake was high during the early days of growth before confluency. It was discovered that inhibition of glucosamine uptake increased with longer exposure to prednisolone, and that uptake was accentuated if the cells were starved for four hr before the radioactive pulse was given. Also, the steroid effect was more pronounced in the S3K strain than in the S3G strain. When glucosamine was added to media containing cells whose alkaline phosphatase levels had been elevated by prednisolone, it was found that the glucosamine completely abolished this increase; in the cells with normally elevated alkaline phosphatase levels, the glucosamine again reduced the level of enzyme. It was pointed out that there is competition between the glucosamine and glucose for uptake by the cell. It is postulated that if glucosamine were to interfere with glucose transport and/or phosphorylation, there would be no increase in sugar phosphate levels, and the subsequent rise in alkaline phosphatase would not take place.

- 1113 DIFFERENCES IN THE QUANTITATIVE DISTRIBUTION OF LYSINE-RICH HISTONES IN NEOPLASTIC AND NORMAL TISSUES. (E.) Kinkade, J. M., Jr. (Baylor Coll. Med., Houston, Texas). *Proc Soc Exp Biol Med* 137(4): 1131-1134, 1971.

Data are presented which show that neoplastic tissues of the rat and calf contain the same lysine-rich histones as normal tissues, and that there are distinct quantitative differences between certain of the corresponding components of neoplastic and normal tissues. Novikoff ascites hepatomas from male rats, and bovine lymphosarcoma, were the sources of neoplastic tissue for the isolation of lysine-rich histones. Lysine-rich histones were extracted from normal and neoplastic tissues, and the crude lysine-rich histone preparation was fractionated by ion-exchange chromatography. A comparison of chromatographic profiles for normal rat liver tissue and Novikoff hepatoma tissue showed that each tissue contained the same complement of lysine-rich histones, but some of the components were present in different amounts in normal and neoplastic tissues. Component 3 of the lysine-rich histone fractions of Novikoff hepatoma tissue contained 41% of the total lysine-rich histone fraction, while component 3 of the lysine-rich histone fractions of normal rat liver tissue contained 32% of the total lysine-rich histone fraction. The crude lysine-rich histone preparation from bovine lymphosarcoma and bovine spleen were fractionated by ion-exchange chromatography. Both tissues contained the same complement of lysine-rich histones,

but increases in certain of the corresponding components, particularly components 1 and 2, were evident in the lymphosarcoma.

- 1114 BIOCHEMICAL MARKERS OF VIRAL ONCOGENESIS WITH SPECIAL REFERENCE TO GLUCOSE TRANSPORT AS A FUNCTIONAL EXPRESSION OF SARCOMA GENES. (E.) Hatanaka, M. (Flow Labs., Rockville, Md.). *Gann* 10:45-73, 1971.

The induction of glucose uptake as a functional expression of a sarcoma gene(s) coincident with morphological changes is reviewed. Infection of cells by C-type RNA viruses containing the sarcoma gene(s) results in transformation generally associated with malignancy. This transformation is accompanied by an enhanced rate of glucose uptake. Changes in glucose uptake appear to be related to the presence of the sarcoma virus genome. Uptake data reveal that virus-infected cells gave  $K_m$  values ten-fold lower than uninfected and leukemia virus-infected mouse cells for transport of glucose, mannose, and galactose; the inverse was obtained with 3-O-methylglucose. Non-permissive cell systems (hamster and human) show no change in sugar transport; rat cells show findings similar to mouse cells after a lag phase. The increased sugar uptake is ascribed to a change in a membrane transport system; in studies with 2-deoxyglucose- $^{14}C$  in MSV-infected cells the uptake was deemed to be due to change in a sugar transport and phosphorylation system. Enhanced sugar uptake, which is directly related to the expression of sarcoma genes, is also seen in sarcoma genes of hamster RNA viruses and chicken RNA viruses. A functional change in membrane-bound sugar transport and transport-associated phosphorylation was seen as an integral event in sarcoma virus transformation. The nature of the alteration of sugar transport is discussed.

- 1115 INDUCTION AND REVERSAL OF CONTACT INHIBITION OF GROWTH BY pH MODIFICATION. (E.) Ceccarelli, C. (Einstein Coll. Med., Bronx, N.Y.) and H. P. Gle. *Nature* 233:271-273, 1971.

The effect of a change of pH upon contact inhibition and growth of cultures is described. In cultures growing at optimal pH, contact inhibition was rapidly induced if the medium was replaced, either by a bicarbonate medium which was acidified (in consequence of cellular metabolism) within hours, or by a medium stabilized at pH 6.9 by appropriate buffers. On the other hand, if cultures which had developed contact inhibition at low population densities were then placed at the optimal pH, growth was reinitiated. Contact inhibition of growth is found in many normal cell strains to be markedly pH-dependent. The three methods of delaying or reversing contact inhibition of growth are: division of the culture to reduce its population density; increasing the concentration of serum which causes renewed synthesis; and, as described here, stabilization of the pH of the medium at the optimal level. The nature of the inhibitory factors responsible for the ultimate cessation of growth even at optimal pH is still to be elucidated. Many cancer cells can grow over a broad pH range and are less susceptible to growth-inhibitory effects.



CHROMOSOME SERIAL STUDIES OF A CULTURED CELL LINE (GH7) FROM A HUMAN LYMPHOSAR- (E.) Brieux de Salum, S. (Nat. Acad. Buenos Aires, Argentina), H. G. Suarez and A. ky. *Rev Europ Etud Clin Biol* 16:711-714, 1971.

pic features of cultured GH7 cells derived human lymphosarcoma are reported. Cytogen- findings described were obtained after 27 month periods up to the 100th *in vitro* passage of cells. The analysis of this lymphoid cell owed cytogenetic features which were compar- many aspects to features of cell lines de- from Burkitt's lymphoma. After 27 months in , the fraction of near-diploid cells found GH7 line in early passages was outgrown by tetraploid cell population which showed wide distribution of chromosome numbers. line showed a clear, nonrandom pattern of and gains in individual chromosome groups. me losses were consistent in chromosome and D, and predominant in chromosome type type chromosomes showed mostly gains. C type omes had mainly chromosome losses in passage mainly gains in passage 42 and 72. In 99% of l karyotypes, throughout all *in vitro* s, a stable feature was a marker chromosome form of a large acrocentric of groups 13-15. sence of a large acrocentric was one feature H7 cells shared with Burkitt's lymphoma

DEOXYRIBONUCLEOSIDE INCORPORATION AND THE ROLE OF HYDROXYUREA IN A MODEL LYMPHOCYTE FOR STUDYING DNA REPAIR IN CARCINOGENESIS. (E.) an, M. W. (U. Pittsburgh Sch. Med., Pa.), S. d E. Farber. *Cancer Res* 31:1307-1312, 1971.

bonucleoside incorporation and the role of hy- rea (HU) during cell damage by alkylation are ed. The incorporation of labeled deoxyribonu- es into acid-insoluble material was determined damage to cultures of human lymphocytes with ni- mustard (HN2) and with methyl methanesulfonate n the presence of HU. Treatment with these agents a six-fold increase in thymidine incorporation as d to controls treated with HU alone. Similar- xycytidine incorporation in the presence of HU ulated following alkylation damage. Deoxyguan- and deoxyadenosine, however, were not stimulated e agents. The results suggest a possible reu- ion of the purine bases for RNA synthesis. In- a of DNA synthesis by both HU and arabinofuran- osine (ara-C) was demonstrated, but, in the case C, no stimulation of thymidine incorporation by g agents was evident. It is suggested that the ts directly at the point of DNA synthesis. imide was used to reveal increased thymidine ration after alkylation. This demonstrates e phenomenon was not dependent on some specific y of HU, since it was also seen with an agent that y inhibits DNA synthesis indirectly, through ition of protein synthesis.

LIFETIME OF THE MESSENGER RNA'S WHICH CODE FOR RIBOSOMAL PROTEINS IN L-CELLS. (E.) N. (Div. Biol. Sci., U. Maryland, Catonsville),

D. E. Kelley and R. P. Perry. *Biochim Biophys Acta* 246(3):493-498, 1971.

An investigation of the metabolic stability (half-life) of the r-protein mRNA's and its comparison with mRNA's specifying other types of protein is presented. The half-lives of the mRNA's were determined in mouse L-cells and the results revealed that the mRNA's for the ribosomal structural proteins have metabolic stabilities comparable to the majority of the mRNA population. Relative lifetimes for ribosomal structural proteins, histones and other proteins were determined by measuring protein synthesis at various time intervals during actinomycin-induced decay of polyribosomal mRNA. The average lifetime for a r-protein message was calculated to be about four hr (about one-fourth of a cell generation), not appreciably different from the average of the bulk of the mRNA, with a half-life of 2.5-3.0 hr. It is suggested that r-protein messages are present throughout the interphase. The histone message is assumed to be processed at a more rapid rate, with a life-time of about 1.5 hr.

1119 AN ANALYSIS OF MALIGNANCY UTILIZING THE DOUBLE HYBRIDIZATION TECHNIQUE. (E.) Oka- da, Y. (Res. Inst. Microbial Dis., Osaka U., Japan), F. Okabayashi and T. Tachibana. *Gann* 10:29-37, 1971.

Inhibition of the tumor-forming capacity of Ehrlich ascites tumor cells by L cell hybrids is described, and an analysis of the reasons for this suppression is presented. Hybrids were developed using Ehrlich ascites tumor cells as one of the parents and skin fibroblasts from C3H or ddO mouse embryos as the other. After fusion with UV-HVJ the hybrids such as CE, dE, and LE were cloned *in vitro*. The hybrids all formed tumors fatal to mice, the tumor-forming capacity was stable and their individual tumor-forming capacity was retained even after *in vivo* passages. Relative inhibition of tumor-forming capacity was measured in terms of a series of hybrid cell lines. These lines contained different ratios of the parental chromosomes formed by two steps of artificial fusion and selected on the basis of morphology, karyological character, surface antigen expressed as antigen complex and as specific antigens, and the characteristics of the hybrid tumors. All hybrids of this series acquired the new characteristics of forming large colonies in soft agar, unlike either parent, and of forming large tumors on the chorioallantoic membrane of chicken eggs. The TFD<sub>50</sub> (50% tumor forming dose) values of each hybrid differed; individual values seemed to be determined by the ratio of L-components to total chromosomes in the hybrids and the effect of L-components on the hybrids was quantitative but not qualitative. Susceptibility of recipients to Ehrlich cells is discussed and the tumor-forming capacity of the various hybrid lines is considered as possibly dependent upon the characteristics specific to L cells.

1120 MODIFICATIONS OF GENETIC INFORMATION IN CROWN-GALL TISSUE CULTURES. (E.) Guille, E. (CNRS Lab., Orsay, France) and J. Grisvard. *Bi- ochem Biophys Res Commun* 44(6):1402-1409, 1971.

Experiments designed to study host reiterative DNA

sequences modified in tumor cells are described. A reiterative fraction of tumor cell DNA was isolated from crown-gall tissue cultures from *Scorzonera hispanica* and *Nicotiana tabacum*. CsCl gradient analyses of tumor cell and healthy DNA were similar; both showed two kinds of molecules: the main DNA (buoyant density = 1.695 g/ml); and a satellite DNA (buoyant density = 1.706 g/ml). Density gradient ultracentrifugation of crown-gall tissue DNA on  $\text{Ag}^+ - \text{Cs}_2\text{SO}_4$  revealed a complex heavy satellite DNA with a density of 1.54-1.57 g/ml; this DNA was not found in healthy tissue. In neutral CsCl, the satellite DNA had a buoyant density of 1.693 g/ml. The satellite DNA renatured completely after heat denaturation and did not separate into complementary strands in alkaline CsCl. It is unlikely that the satellite DNA is an artefact produced by an aggregation of native DNA.

- 1121 RNA METABOLISM IN MOUSE MYELOMA CELLS.  
(E.) Muto, M. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan) and T. Morita. *Gann* 62(2): 107-119, 1971.

A study of the dynamics of RNA in mouse myeloma cells (X5563) which were producing  $\gamma$ -globulin continuously, is described. Rapid labeling was performed by incubation with  $^{32}\text{P}$  orthophosphate, the cell nucleus and cytoplasm were separated, RNA was extracted and analyzed, and the base composition of the various labeled RNA fractions was determined. It was found that RNA of myeloma cells could be synthesized at a constant rate during the *in vitro* incubation for five hr. During the first 30 min, 45S RNA was synthesized and 32S, 28S and 18S appeared later. Treatment of 45S RNA with DNase, protease, or removal of  $\text{Mg}^{2+}$ , produced no change in sedimentation, but 45S RNA was completely destroyed by RNase. These results demonstrated the existence of continuous polynucleotide chains of 45S. An outstanding characteristic in the base composition of the various RNA species was the high guanylic and cytidylic acid contents. The synthesis of rapidly labeled 60-80S and 45S RNA was highly inhibited by actinomycin-D, but the transition of 45S and 32S RNA in the nucleus was not inhibited. The suppressive effect of actinomycin-D on the transfer of 18S and 28S RNA from the nucleus to the cytoplasm seemed to result from the suppression of protein synthesis by the inhibition of RNA synthesis. It was suggested that the transfer of ribosomal RNA from the nucleus to cytoplasm required newly synthesized proteins.

- 1122 PRIMARY POLYCYTHEMIA: 2. TYPES OF CHROMOSOME ABERRATIONS IN 21 CLONES FOUND IN BONE MARROW SAMPLES FROM 50 PATIENTS. (E.) Visfeldt, J. (Com. Hosp., Copenhagen, Denmark). *Acta Path Microbiol Scand A* (79):513-523, 1971.

Clone formations, karyotypic features, and chromosomal aberrations of bone marrow cells from 50 patients with primary polycythemia (PP) are described. Subjects included untreated patients, treated patients with and without myelofibrosis, and treated patients in whom transition to a leukemic phase was suspected. Of bone marrow specimens from the 50 patients, 21 presented large clone formations; these 21 clones

were all found in treated patients. Of bone marrow specimens from 23 treated patients with myelofibrosis, nine presented clones; and of specimens from untreated patients suspected to be in transition to a leukemic phase, five presented clones. Karyotype studies indicated that in three clones the karyotypes were aneuploid; the remaining 18 clones had diploid karyotypes. Although four of the 18 diploid clones were considered to have balanced karyotypes, it was not possible to determine this with certainty. In six cases a deleted F-group chromosome was the only chromosomal aberration found in the clones; in another two cases, a deleted F-group chromosome was associated with other abnormalities, including trisomy C and deleted C- and D-group chromosomes. No fundamental differences were found between karyotypes of clones from PP patients who subsequently died with leukemia and karyotypes of clones from other PP patients.

- 1123 ULTRASTRUCTURAL AND BIOCHEMICAL STUDY OF NEUROBLASTOMA AND GANGLIONEUROBLASTOMA. (E.) Yokoyama, M. (Fac. Med., U. Tokyo, Japan), K. Okada, A. Tokue, H. Takayasu and R. Yamada. *Invest Urol* 9(2):156-164, 1971.

Investigations of the ultrastructure, histochemistry and biochemistry of five neuroblastomas and of one ganglioneuroblastoma are reported. The neuroblastoma cells usually possessed cytoplasmic processes and polymorphic nuclei containing nucleochromatin. In the cytoplasm of large tumor cells rough endoplasmic reticulum, free ribonuclear protein particles, microfilaments, microtubules, long cytoplasmic processes, and oval mitochondria were seen. No Schwann's cells were found in the five tumors but in some cases, round nuclei with insignificant nucleochromatin, lysosomes and rough endoplasmic reticulum in the cytoplasm, as well as extremely indented plasma membranes were seen. In the ganglioneuroblastoma, ganglion cells, a network of numerous nerve processes and Schwann's cells, and cells with rough endoplasmic reticulum were observed. Catecholamines varied in quantity in the different tumor tissue. Large quantities of amines, comparable to those in pheochromocytoma, were found in one neuroblastoma. Urinary adrenaline and noradrenaline were not elevated. Total metanephrine was high in two cases and a large amount of dopamine was detected in another. Catecholamine synthesis and storage in these tumors are discussed.

- 1124 EXPRESSION OF THE MITOCHONDRIAL GENOME IN HEPAROMA CELLS: VI. SIZE DETERMINATION OF MITOCHONDRIAL RIBOSOMAL RNA BY ELECTRON MICROSCOPY. (E.) Robberson, D. (Div. Biol., California Inst. Tech., Pasadena), Y. Aloni, G. Attardi and N. Davidson. *J Molec Biol* 60(3):473-484, 1971.

Length measurements of the two mitochondrial specific ribosomal RNAs of HeLa cells are reported. RNA molecules were mounted for electron microscopy by a modified basic protein film method under strongly denaturing conditions. Length measurements on purified 12S and 16S mitochondrial rRNA, on mixtures of 16S with 12S RNAs, and on mixtures of 12S with 18S



plasmic rRNA, were carried out. The 12S RNA is considerably shorter (0.27  $\mu$ ) than the 18S RNA (0.42  $\mu$ ), and the 16S RNA (0.42  $\mu$ ) was somewhat shorter than the 18S RNA. The molecular wt of 18S plasmic rRNA had been measured as  $0.71 \times 10^6$  by sedimentation equilibrium. Assuming that these molecular lengths were proportional to molecular wt, molecular wts for the 12S and 16S mitochondrial rRNAs were  $0.35 \times 10^6$  and  $0.54 \times 10^6$ , resp. The values for molecular wt were not in agreement with those arrived at by gel electrophoresis, but in good agreement with molecular wt values calculated from sedimentation velocity measurements.

**INCLUSION BODIES IN HUMAN PRIMARY LIVER CARCINOMA.** (E.) Kendrey, G. (Laszlo Hosp., Budapest, Hungary). *Acta Morph Acad Sci Hung* 18(4): 301, 1970.

Paraneoplastic and cytoplasmic inclusion bodies found in sections from 68 primary liver carcinomas are described; autopsy materials included 65 hepatocellular carcinomas and three cholangiocellular carcinomas. Nuclear inclusions were found only in hepatocellular carcinomas and in 42 of the 65 cases. Inclusions occurred for the most part in anaplastic areas of the tumors; these areas contained abundant cells in which most of the inclusions were found. The intranuclear inclusions stained like nucleoli and were surrounded by a basophilic membrane having the thickness of the nuclear envelope. Cytoplasmic inclusions were presumably cytoplasmic indentations and not true inclusions. Like intranuclear inclusions, cytoplasmic inclusions were found only in hepatocellular carcinomas (22 of the 65 hepatocellular tumors had cytoplasmic inclusions). Cytoplasmic bodies usually occurred in groups, stained well with acid dyes, and were often more basophilic than the cytoplasm itself. Cytoplasmic inclusions were usually seen in anaplastic areas of the tumors; they were intensely PAS-positive and were probably caused by focal cytoplasmic degeneration. Three unusual types of cytoplasmic inclusion bodies were seen: an inclusion resembling a shell within an open shell; a radial structure; a body with spoke-like spiculiform processes radiating from the center toward surrounding cytoplasm. The altered metabolism of tumor cells may account for these unusual forms of inclusion; these inclusions were thought to be pathologic products of the results of degeneration.

**TRANSFER RNA'S AND HUMAN LYMPHOCYTE TRANSFORMATION.** (E.) Rigby, P. G. (U. Nebraska Coll. Med., Omaha). *J Lab Clin Med* 78(4): 50, 1971.

Experiments designed to document the stimulatory and suppressive effect of the three different monoclonal transfer RNAs (tRNA) on human lymphocytes in tissue culture at varying doses, with or without phytohemagglutinin (PHA) are reported. The effect of tRNAs on lymphocyte transformation was measured by uptake of  $^3\text{H}$ -thymidine by cells treated with the tRNAs. The individual tRNA for Phe showed significant suppression of PHA-stimulated human

lymphocyte transformation at  $5.0 \times 10^{-2}$  mg/2 cc of culture; at this dosage, tRNA for Phe reduced lymphocyte transformation to 60% of control values. The suppressive effect of the tRNA for Phe tended to diminish at decreasing concentrations in the presence of PHA. The tRNAs (Phe, Glu, Arg) sometimes showed an effect in otherwise unstimulated cultures at a dose of  $5.0 \times 10^{-6}$  mg; this stimulation in  $^3\text{H}$ -thymidine uptake by lymphocytes varied in degree with different lymphocyte donors. The highest observed uptake of  $^3\text{H}$ -thymidine in individual experiments at a dose of  $5 \times 10^{-6}$  mg was 156% of control values with tRNA (Phe), 159% of controls with tRNA (Arg), and 141% of controls with tRNA (Glu). No extra stimulation of lymphocyte transformation was effected by the presence of PHA.

**1127 NUCLEOLAR PROTEIN METABOLISM IN ACTINOMYCIN D TREATED HeLa CELLS.** (E.) Maisel, J. C. (Dept. Molec. Cell. Develop. Biol., U. Colorado, Boulder) and E. H. McConkey. *J Molec Biol* 61(1):251-255, 1971.

An investigation to determine whether newly synthesized ribosomal proteins accumulate in the nucleoli when precursor RNA synthesis is selectively inhibited by actinomycin D is presented; the importance of determining the site of synthesis of ribosomal proteins is emphasized. HeLa cells and controls, treated with actinomycin D, were incubated with 18 labeled amino acids and nucleolar incorporation was evaluated. The level of amino acid incorporation with regard to control nucleoli and cytoplasm increased at the same rate, while that of nucleoli treated with actinomycin D had less incorporation than control nuclei. SDS gel electrophoresis showed a similar and increasing pattern in compared ribosomal and nucleolar proteins. Quantitatively less protein was found in the nucleoli of treated cells as compared to controls. The results indicated that newly made ribosomal proteins accumulate rapidly in the nucleoli of control cells but not in the actinomycin D-treated cells. It is submitted that while the synthesis of ribosomal proteins does proceed in the absence of ribosomal RNA synthesis, the nucleolus no longer contains binding sites to serve as a point of accumulation for ribosomal proteins.

**1128 STUDIES ON PLASMA MEMBRANES: XIV. ADENYL CYCLASE IN PLASMA MEMBRANES ISOLATED FROM RAT AND MOUSE LIVERS AND HEPATOMAS, AND ITS HORMONE SENSITIVITY.** (E.) Emmelot, P. (Netherlands Cancer Inst., Amsterdam) and C. J. Bos. *Biochim Biophys Acta* 249(1):285-292, 1971.

The use of well-characterized plasma membranes isolated from rat or mouse liver and the carrying out of an accurate assay system is described. Plasma membranes from male rats with transplanted hepatomas, originating from female rats fed with 4-dimethylaminoazobenzene, and those from transplanted mouse hepatomas, spontaneously formed, were studied. The enzyme assay was carried out in the presence of the ATP regenerating system, phosphoenolpyruvate and pyruvate kinase. The adenylyl cyclase activity in terms

of cyclic adenosine 3',5'-monophosphate (AMP) formed from ATP was about 2.3 nmoles/mg membrane protein/h; glucagon, epinephrine and fluoride enhanced this activity under certain conditions. Results on two representatives of the liver-hepatoma model revealed differences in metabolic characters according to differentiation status and growth rate. Rat hepatoma membranes exhibited very low adenyl cyclase activity and the relative stimulation of glucagon and epinephrine was either lower (glucagon) or absent (epinephrine) in the hepatoma membrane of the rat; no such differentiation was seen in the mouse liver and hepatoma. The relationship of the adenyl cyclase system to neoplastic disease is discussed.

- 1129 CHANGES IN HISTONE PHOSPHORYLATION AND ASSOCIATED EARLY METABOLIC EVENTS IN PIG LYMPHOCYTE CULTURES TRANSFORMED BY PHYTOHEMAGGLUTININ OR 6-N,2'-O-DIBUTYRYLADENOSINE 3':5'-CYCLIC MONOPHOSPHATE. (E.) Cross, M. E. (Dept. Biochem., U. Oxford, England) and M. G. Ord. *Biochem J* 124:241-248, 1971.

The specific radioactivity of  $P_i$  and ATP in pig lymphocyte cultures, immediately after stimulation in the presence of  $(^{32}P)P_i$  is examined for a relationship in the latter to changes in the specific radioactivities of the phosphate groups on histones. Activities of histone kinase and phosphatase were also assayed. Stimulation of pig lymphocyte cultures by either phytohemagglutinin or dibutyl cyclic AMP (6-N,2'-O-dibutyladenosine 3':5'-cyclic monophosphate) resulted in an immediate increase in  $P_i$  and a slight fall in ATP concentration. After 30-40 min the specific radioactivity and net ATP content of the cells exposed to  $(^{32}P)P_i$  began to increase, continuing for 20-30 min. Chlorpromazine prevented this action with phytohemagglutinin but not with cyclic AMP. It is suggested that the increase in  $P_i$  is due to metabolic effects of cyclic AMP and is not dependent upon membrane changes produced by the mitogen. During the first 30 min after stimulation,  $(^{32}P)P_i$  was incorporated into histone, decreasing in histone F1 after 30 min and increasing in the other histone fractions. Histone kinase activity paralleled the  $(^{32}P)P_i$  incorporation results 30 min after stimulation when either histone F1 or other histones were used as substrate; after 30 min kinase activity in histone F1 decreased; kinase activity increased in activity with the other histones up to 60 min, then fell. Phosphatase activity behaved similarly. The results suggest that cyclic AMP activation of histone kinase is one of the early events occurring after stimulation.

- 1130 TRANSLOCATION OF DNA FROM THE VASCULAR INTO THE NUCLEAR COMPARTMENT OF SOLID MAMMARY TUMORS. (E.) Watters, C. (Nat'l. Cancer Inst., Nat'l. Inst., Hlth., Bethesda, Md.) and P. M. Gullino. *Cancer Res* 31:1231-1243, 1971.

The principal objective of this work was to ascertain whether large fragments of tritiated DNA added to the blood stream could reach the nuclei of solid tumors. Labeled DNA was prepared by injecting Sprague-Dawley female rats in the seventh to the tenth day of lactation with tritiated methyl-thymidine; after 18 to 24 hr, the mammary glands were removed and treated to yield a DNA homogenate. This DNA homogenate, or

homogenate obtained from *Micrococcus lysodeikticus*, was arterially infused into Sprague-Dawley three month old rats which were infected with Walker carcinoma 256. In *ex vivo* studies, the molecular weight profile (MWP) showed a minor shift when labeled DNA was added to the blood alone; but when a tumor was added to the circuit, larger shifts in MWP's were observed both in the tritiated DNA in the blood and in the part incorporated in the tumor. DNA uptake by the tumor corresponded to .25% to .50% of the total tumor DNA and was an exponential function of tumor weight within the limits of 5 g to 10 g. In addition, 80% of the labeled DNA was concentrated in the cell compartment, with formation of two radioactive gradients between the vascular and interstitial space and between the interstitial space and cellular compartment. *In vivo* studies confirmed the *ex vivo* findings and yielded the following additional information: 80% of the labeled DNA in the cells that were measured was limited to the nucleus. Various biochemical tests also showed that small-molecular-weight labeled DNA constituted the largest fraction present in the tumor interstitial fluid, probably because the larger fragments are the ones actively concentrated by the cells. When the size of the tritiated DNA fragments infused was the largest, the amount of high-molecular-weight labeled DNA isolated from the tumor nuclei was the highest. Since autoradiographic techniques failed it cannot be said whether tritiated DNA was accumulated in the nuclei of neoplastic or stroma cells. However, it seems most probable from the data that the large tritiated DNA fragments penetrated into the nuclei of neoplastic cells.

- 1131 ELECTRON MICROSCOPIC STUDY OF SPONTANEOUS MAMMARY CARCINOMAS IN CATS AND DOGS: VIRUS-LIKE PARTICLES IN CAT MAMMARY CARCINOMAS. (E.) Feldman, D. G. (VA Hosp. Bronx, N.Y.) and L. Gross. *Cancer Res* 31:1261-1267, 1971.

Electron microscopic examinations for the presence of virus-like particles in spontaneous mammary tumors of cats and dogs are reported. Material included 11 spontaneous cat mammary carcinomas (eight adenocarcinomas) and 11 spontaneous dog carcinomas (6 adenocarcinomas). Virus-like particles were present in five cat tumors. The particles were spherical with electron-lucent centers and several concentric shells. They varied slightly in morphology and location within the cell. In three of the tumors, particles with two concentric shells were seen; the inner shell appeared more electron dense than the outer shell. The average diameter of the particles was 90 mμ. These particles were located within the cisternae of the endoplasmic reticulum and in the perinuclear cisternae of epithelial cells. Some particles appeared to bud from the membranes of the endoplasmic reticulum into the interior of the cisternae. In one tumor, virus-like particles with four concentric shells were seen. These particles appeared to bud from the membranes of epithelial cells and were also seen free within the intercellular spaces. A fifth tumor contained both types of particles described above. It was not clear whether the particles in the cat tumors were causally related to those tumors, or whether they were merely passenger agents in the tumors.



virus-like particles were found in spontaneous primary tumors of dogs.

2 INTRACELLULAR COMPONENTS OF NEOPLASTIC AND NORMAL ALVEOLAR CELLS FROM MOUSE LUNGS: QUANTITATIVE ULTRASTRUCTURAL COMPARISON. (E.) Toks, R. E. (U. Oregon Med. Sch., Portland) and Adkison. *J Nat Cancer Inst* 47(3):639-644, 1971.

cellular components of lung alveolar tumor cells of normal alveolar cells are quantitated and compared electron microscopically. Normal type B alveolar cells came from normal A/He mice and alveolar tumor cells of the mouse lung came from A/He mice given urethan in drinking water. Approximately 9  $\mu^2$  of type B alveolar cells and 3192  $\mu^2$  of tumor cells were evaluated using electron micrographs and a square-grid overlay. Type B alveolar cells had a nucleus/cytoplasm volume ratio of 0.356 and tumor cells had a ratio of 0.590. Mitochondria occupied 17% of type B cell cytoplasm and 11% of tumor cell cytoplasm. Cytosomes comprised 24.5% of type B cell and 12% of tumor cell cytoplasm. Nuclear endoplasmic reticulum occupied 41% of type B cell and 26.5% of type B cell cytoplasm. Nucleoli, heterochromatin occupied 33% of type B cell nucleoplasm and 22.5% of tumor cell nucleoplasm. Euchromatin comprised 72% of tumor cell and 63.5% of type B cell nucleoplasm. Nucleoli constituted 1% of tumor cell and 3% type B cell nucleoplasm. The ratio of euchromatin/heterochromatin for type B alveolar cells was 1.95; for tumor cells, this ratio was 3.20.

3 GROWTH REGULATION IN MOUSE EPIDERMIS: I. G<sub>2</sub>-INHIBITOR PRESENT IN THE BASAL LAYER. (E.) Elgjo, K. (Rikshosp., Oslo, Norway), O. D. Laerum and W. Edgehill. *Virchows Arch Abt Zellpath* 8:277-283, 1971.

Experiments are reported which are designed to test the hypothesis that epidermal chalone (a growth inhibitor) is produced by differentiating epidermal cells and inhibits the mitotic rate of basal cells. Differentiated cells of normal three month old hr/hr mice were separated from the basal cells by trypsin treatment. Water extracts from the two cell types were examined for their mitosis-inhibiting effect *in vivo* on dorsal skin of hairless mice by means of the Colcemid technique. Extracts from untreated whole mouse skin and from trypsin-treated skin depressed the mitotic rate by about 70%; water extracts of isolated dermis did not affect epidermal mitotic rate. Lyophilized water extracts of basal cells inhibited the epidermal mitotic rate by 56-75%. Only a certain proportion of cells in G<sub>2</sub> seemed to be susceptible to the inhibitory effect of epidermal chalone. Extracts of differentiating cells had a varying and insignificant inhibitory effect on the epidermal mitotic rate. Results suggested that the basal cells of normal mouse epidermis contain an agent possessing a very strong inhibiting effect on the epidermal mitotic rate; since extracts made from other organs have no inhibiting effect on mitotic rate when injected in similar doses, this agent was thought to be tissue-specific.

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**Editor**

Robert Love, M.D.  
Jefferson Medical College, Philadelphia

**Associate Editor**

George P. Studzinski, M.D.  
Jefferson Medical College, Philadelphia

**NCI Staff Consultants**

Elizabeth Weisburger, Ph.D.

Sidney Siegel, Ph.D.

Louis P. Greenburg, M.S.

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LONDON



## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain two-hundred abstracts and twenty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

*Carcinogenesis Abstracts* is normally published monthly. Volume IX covers the scientific literature published from July 1970 through June 1971. A cumulative subject and author index for Volume IX will be published shortly after the final regular issue. This journal is available free of charge to libraries and to individuals who have a professional interest in carcinogenesis. Requests for *Carcinogenesis Abstracts* from qualified individuals should include statements of their relationship to carcinogenesis research. All correspondence should be addressed as follows:

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## NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

### LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
ln.	Indonesian	Viet.	Vietnamese

### ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram ( $10^{-9}$ )
CNS	central nervous system	pg	picogram ( $10^{-12}$ )
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	U	unit(s)
kg	kilogram(s)	UV	ultraviolet
LD <sub>50</sub>	median lethal dose(s)	WBC	white blood cells (leukocytes), white blood count
m	meter(s)	wk	week
M	molar	wt	weight
mEq	milliequivalent(s)	yr	year(s)
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		





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01 EXPERIMENTALLY INDUCED GASTRIC ADENOCARCINOMAS: MAUDE ABBOTT LECTURE, 1971. (E.) Stewart, H. L. (Natl. Inst. Hlth., Bethesda, Md.). *Invest* 25(6):672-674, 1971.

The role of 3-methylcholanthrene (3-MC), *N,N'*-2,7-dimethylfluorenylbisacetamide (2,7-FAA), *N*-2-fluorenylacetamide (2-FA), irradiation, aflatoxins, elaiomycin, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), 2,2-dimethylbenzanthracene (DMBA) and *N*-methyl-*N*-nitroso-*N'*-acetylurea (MNAU), alone or in combination, in the production of stomach adenocarcinoma of experimental animals is reviewed. Injection of 3-MA into the stomach wall or feeding 2,7-FAA p.o. were the first methods used to induce stomach cancer. 3-MA and 2,7-FAA used simultaneously were synergistic. The types of lesions induced by 3-MC and 2,7-FAA, their incidence and sites of occurrence in the stomach were discussed. MNAU has recently been shown to induce a much higher incidence of gastric adenocarcinoma than either 3-MC or 2,7-FAA. A major problem of many of the carcinogens used to induce gastric cancer is the fact that they may also induce tumors at extragastric sites. This was especially a problem with 2,7-FAA. Another major problem in work on gastric cancers was that a set of criteria for the histologic diagnosis of these carcinomas which will differentiate them from atypias of gastric tissue has not been set down. (7 references)

HISTOCOMPATIBILITY, IMMUNE RESPONSE, AND TUMOR INDUCTION: SPECIFIC IMMUNE RESPONSE S. (E.) Benacerraf, B. (Harvard Med. Sch., Boston, Mass.), I. Green, H. G. Bluestein and L. A. (E.) *Transplantation Proc* 3(3):1327-1331, 1971.

Inbred guinea pig strains (2 and 13, developed by Hartley and Hartley random-bred lines were used to determine specific immune responsiveness. Three genes were identified in the guinea pig strains responsible for responsiveness to poly-L-lysine, poly-L-glutamic acid, copolymers of L-glutamic acid and L-lysine, haptens conjugates of these polypeptides; 2) the gene, which controls responsiveness to L-glutamic acid and L-alanine; and 3) the GT gene, which controls responsiveness to a copolymer of L-glutamic acid and L-tyrosine. The first two genes are found in strain 2 but not in strain 13 in inbred animals; the GT gene is found in strain 13 but not in strain 2. In random-bred Hartley animals, the GT gene segregates from PLL and GA responsiveness. Three strains were injected to determine if a particular gene was necessary for responsiveness to bovine serum albumin (BSA) in low doses. Strain 2 expressed linkage in the genes controlling responsiveness to PLL antigens, GA, and low doses of BSA; strain 13 did not respond. In random-bred animals, recombination may have occurred between the PLL gene and the GA and BSA gene, since two responses were observed, one resembling strain 2 and the other resembling strain 13. Random-bred Hartley guinea pigs were tested for the presence of a strain 2 specificity on their lymphocytes to determine if immune response genes are identical with genes controlling individual histocompatibilities or are very

closely linked with them. Possession of the PLL gene was associated with susceptibility to lysis of the cells by antiserum of antistrain d; cells from PLL-negative animals were not susceptible to lysis by the antiserum. Responsiveness to antigens under control of specific immune response genes is accompanied by antibody responses to haptens they bear, illustrating the gene-controlling carrier function. Conversely, it was discovered after further experiment that an antigen such as DNP-PLL can stimulate specific antibody synthesis in the absence of cellular immunity in animals lacking the PLL gene if it is administered bound to an immunogenic carrier. (19 references)

1203 EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON TUMOR CELL MEMBRANES. INTRODUCTION: BIOLOGICAL FEATURES OF CELL SURFACE ANTIGENS. (E.) Haughton, G. (Sch. Med., U. North Carolina, Chapel Hill, N.C.). *Transplantation Proc* 3(3):1147-1149, 1971.

Some of the biological similarities and differences between tumor specific transplantation antigens (TSTA) and normal histocompatibility antigens (NHA) are reviewed. TSTA, unlike NHA, are tissue specific. However, this distribution may not be completely valid, as it has been suggested that TSTA of chemically induced tumors may represent reexpression of embryonic antigens. TSTA are considered "weak" antigens since induced immunity against them may be overcome by challenging with a large dose of tumor cells. Some NHA are "strong" in that they are not easily overwhelmed. TSTA are able to evoke an immune response in the primary autochthonous host while NHA do not. There are several similarities between TSTA and NHA. Both are very, although not absolutely, stable in culture or after repeated *in vivo* transplantation. Both types of antigen fluctuate in phase with the cell's mitotic cycle. Both frequently do not evoke a graft rejection response, although they are capable of doing so, particularly under experimental conditions. Both antigens induce cellular and humoral responses leading, respectively, to graft rejection and immunologic enhancement. An allograft usually causes rejection *in vivo* whereas enhancement often occurs with many primary tumors. In general, NHA evoke a rejection response and TSTA evoke enhancement. Under normal conditions, the humoral and cellular responses are balanced so as to favor immunologic enhancement. (14 references)

1204 THE POLYMORPHISM OF THE HL-A SYSTEM. (E.) Dausset, J. (Hosp. St. Louis, Paris, France). *Transplantation Proc* 3(3):1139-1146, 1971.

Factors governing polymorphism of the HL-A antigen system are discussed. Such points as the international designations for specificities of the first and second loci and their serological interrelationships are reviewed in detail. The article concludes with a proposed study to show a correlation in man similar to that found in mice between susceptibility to oncogenic viruses and an H-2 system. (28 references)

- 1205 THE CONTROL OF NONVIRION ANTIGENS INDUCED BY PAPOVAVIRUSES. (E.) Rapp, F. (Milton S. Hershey Med. Ctr. Pennsylvania State U., Hershey,) and N. A. Crouch. *Transplantation Proc* 3(3):1175-1178, 1971.

The immunologically specific nonvirion antigens induced during infection of cells by the oncogenic papovaviruses, SV40, polyoma and many papilloma viruses, are briefly reviewed and evidence on whether their synthesis is controlled by the host or viral genome is discussed. The tumor (T) antigens, detected by complement-fixation and immuno-fluorescence tests, are usually found in the nucleus, although they have been observed in the cytoplasm. Their biologic function is unknown. T antigens appear to be heat-labile proteins and have been partially purified from SV40-transformed cells. T antigen formation is detected early in infection prior to synthesis of the capsid antigen. Its appearance is dependent upon RNA and protein synthesis but not upon DNA synthesis. Surface (S) antigen is associated with the membrane of cells transformed by both SV40 and polyoma virus; its biologic function is also unknown. One report that S antigen has been isolated from membranes of both normal and polyoma-transformed cells by proteolytic enzymes may cast some doubt as to its relevance to viral oncogenesis. Tumor specific transplantation antigens (TSTA), also membrane-associated, are detected by *in vivo* tumor cell transplantation tests. The suggestion that TSTA is related to "tumor specific" agglutinin sites seems unlikely. DNA transcription and protein synthesis are required for TSTA formation. It is not known whether the DNA transcribed is viral or cellular. Available information suggests that TSTA and S antigen are not identical. Literature reviewed suggests that biosynthesis of the nonvirion T antigen and TSTA are controlled by the viral genome. S-antigen, on the other hand, may be controlled by the host cell. However, all data have so far been inconclusive concerning control of antigen synthesis in papovavirus-infected cells. (23 references)

- 1206 THE MODIFICATION OF IMMUNOLOGIC SPECIFICITY AND FUNCTION OF CELLULAR MEMBRANES BY HERPESVIRUSES. (E.) Roizman, B. (Dept. Microbiol. Biophys., U. Chicago, Ill.) *Transplantation Proc* 3(3):1179-1183, 1971.

A summary of the work done over the past several years on the mechanism by which herpesviruses modify the internal membrane and the plasma membrane of cells they infect is presented. The review discusses: 1) evidence that internal membranes are altered by a two-step modification in which there is a generalized change shown by immunologic specificity, and a modification of membranes connected with the envelopment of the nucleocapsids; 2) evidence that the external membranes are modified as shown by a change in the social behavior of infected cells; 3) immunologic studies which indicate that the new antigen on the infected cell surface is the same or related to the antigen present on the surface of the envelope of the viron; and 4) genetic evidence for the role of virus-specific membrane antigen in specifying

social behavior of infected cells. Evidence of the chemical basis of membrane-specific products specified by herpesviruses studied over a two- to three-year period showed that the membrane glycoproteins are: 1) specified by the virus; 2) bound specifically to membranes; 3) selective; and 4) conferring a new immunologic specificity to the isolated smooth membrane. The function of membrane glycoproteins in specifying social behavior of infected cells was shown in a series of experiments with doubly infected strains of HSV (Herpes simplex virus); equal amounts of each trait were produced in the virus progeny but the dominant trait remained dominant with respect to social behavior and membrane glycoproteins specified. (13 references)

- 1207 HOST-GENE CONTROL OF C-TYPE TUMOR VIRUS-EXPRESSION AND TUMORIGENESIS: RELEVANCE OF STUDIES IN INBRED MICE TO CANCER IN MAN AND OTHER SPECIES. (E.) Meier, H. (Jackson Lab., Bar Harbor, Me.) and R. J. Huebner. *Proc Nat Acad Sci* 68(11):2664-2668, 1971.

C-type RNA viruses, which are tumorigenic in mice and other animals, are transmitted from one generation to another in association with the host-cell genome. Tumorigenesis involves both genetic and environmental factors. Although single-locus determination of oncogenic activity is most likely the exception, specific genes which have a major effect have been identified both in inbred mice and in man. New and existing data concerning host-gene controls of virus-genome and of tumor expression in mice are presented and their relevance to cancer induction in man is discussed. The fact that neoplasia is associated with several heritable disorders indicates that genetic factors are probably operative in man as they are in mice. Investigation of these relationships may lead to recognition of etiological relationships and understanding of host-gene controlled oncogenic mechanisms. The presence of C-particles in human tumors suggests that oncogenes may exist in humans which are similar to those of C-type viruses studied in mice. (71 references)

- 1208 SOME NEGLECTED LEADS TO CANCER CAUSATION. (E.) Burkitt, D. P. (Med. Res. Council, London, England). *J Nat Cancer Inst* 47(5):913-919, 1971.

An assumption can be made that diseases which tend to be associated may have a common or related cause. Various benign and malignant diseases were reviewed and compared to determine if related diseases could elucidate the etiology of various neoplasms. Several examples of related diseases are presented. It is emphasized that a distinction must be made between conditions which are a consequence of diseases and conditions which are related to other diseases because of common etiological factors. Cleave's hypothesis relating the increased incidence of many diseases to increased dietary use of refined carbohydrates and cereals is discussed in relation to the incidence of bowel cancer. Mechanisms relating



vel cancer to other noninfective diseases are also discussed. (23 references)

9 NUCLEAR ACIDIC PROTEINS AND CELL PROLIFERATION. (E.) Baserga, R. (Temple U. Sch., Philadelphia, Pa.) and G. Stein. *Fed Proc* 6(6):1752-1759, 1971.

vidence suggesting that acidic nuclear proteins are involved in the control of gene expression in mammalian cells, and, specifically, in the response of quiescent cells to stimuli which initiate cell proliferation, is reviewed. Gene activation appears to be a crucial step in the sequence of events leading to the onset of DNA synthesis and cell proliferation in quiescent cells. Models of stimulated DNA synthesis which have been extensively studied include regenerating liver after partial hepatectomy *in vivo*, the estrogen-stimulated uterus, phytohemagglutinin-stimulated lymphocytes *in vitro* and stationary cell cultures infected with oncogenic DNA viruses. The mechanism by which the stimulus to proliferate activates the cell genome may involve repression or derepression of the mammalian cell genome by regulating molecules acting on DNA and slowing or inhibiting its transcription. Histones are often thought to be the gene regulators of mammalian cells and are thought to be capable of affecting DNA transcription. However, two findings state against the hypothesis that histones are regulators: (1.) histones have no tissue or species specificity; and (2.) histones are present in similar amounts in active and inactive tissues. Acidic nuclear proteins have been considered as possible gene regulators in mammalian cells. Evidence that acidic nuclear proteins act to regulate gene activity includes: (1.) the finding that active tissues contain more acidic nuclear proteins than inactive tissues; (2.) the finding that active chromatin contains more acidic nuclear proteins than inactive chromatin; (3.) the finding that acidic nuclear proteins restore histone-inhibited dependent RNA synthesis *in vitro*; (4.) the finding that acidic nuclear proteins are actively synthesized following stimulation of cell division. Recent findings also indicate that acidic nuclear proteins may be important in models of stimulated DNA synthesis. (157 references)

MAMMALIAN CELL TRANSFORMATION *IN VITRO* BY MEANS OF CHEMICAL CARCINOGENS. (Rus.) I. S. (Acad. Med. Sci. USSR) and I. I. Parkhomenko. *Vop Onkol* 17(6):106-115, 1971.

cedures applied in chemical carcinogenesis *in vitro* are reviewed with an emphasis on monolayer and clonal culture methods. Included are discussions of the most important works related to malignant transformation of primary mammalian cell clones following exposure to carcinogens such as 3,4-benzo(a)pyrene, methylcholanthrene, 7,12-dimethylbenz(a)anthracene and nitrosomethylurea. Toxicity of these compounds constitutes another topic. Reference is made to optimal concentrations required for maximum transfor-

mation yields and to the enhancing role played by surface-active agents such as Tween 80 in the initiation of the transformation effect. The rate of appearance and yields of transformed cells characterized by both the morphologic (loss of contact inhibition) and biologic (oncogenicity *in vivo* upon inoculation into homologous animals) features of transformation suggest a direct process, induced by the chemical carcinogen. No "pretumorous cells" are thought to be present in primary cultures. A wide range of yet unknown answers regarding conditions required for transformation is discussed. The question of the activating role played by the chemical carcinogen upon an existing latent virus within the cell is not treated, due to insufficient evidence. (68 references)

1211 SOME ASPECTS OF CANCER OF THE STOMACH. (E.) Thomson, J. W. W. (Roy. Infirm., Edinburgh, Scotland), A. B. MacGregor and D. A. D. Macleod. *J Roy Coll Surg Edinb* 16(5):287-298, 1971. (16 references)

1212 COMPARATIVE VIROLOGY OF PRIMATES. (E.) Kalter, S. S. (Southwest Fdn. Res. Educ., San Antonio, Texas) and R. L. Heberling. *Bact Rev* 35(3):310-364, 1971. (361 references)

1213 CELLULAR CHANGES IN CHRONIC MYELOID LEUKAEMIA. (E.) Pedersen, B. (Dept. Med., U. Cambridge, England) and F. G. J. Hayhoe. *Brit J Haemat* 21(3):251-256, 1971. (50 references)

1214 HOW SMOKING CAUSES LUNG CANCER. (E.) Rusk, H. S. (Pueblo, Colo.). *Rocky Mountain Med J* 68(10):37-39, 1971. (7 references)

1215 CANCERS OF THE PANCREAS. (Fr.) Coulbois, J. (Ambroise-Pare Hosp., Boulogne, France) and P. Dupuy. *Rev Med* 12(30):1863-1870, 1971. (No references)

1216 VITAMIN B 12 AND TUMOR DEVELOPMENT. (Fr.) Chauvergne, J. (No affiliation), B. Hoerni, A. Hugues, C. Lagarde, A. Le Treut, D. Maree and J. Touchard. *Produits Problems Pharmaceutiques* 26(8):562-563, 1971. (No references)

1217 LUNG CANCER. (It.) D'Errico, G. (Inst. Tumor Stud. Ther., Naples, Italy). *Riforma Med* 84(42):1149-1154, 1970. (No references)

1218 THE ELUCIDATION OF THE FREUND-NEUBERG CYTOLYTIC PHENOMENA LEADS TO NEW CONSIDERATIONS ON IMMUNE REACTIONS AGAINST CANCER. (Ger.) Christiani, A. (No affiliation). *Oest Z Erforsch Bekaempf Krebskrankh* 26(4):255-265, 1971. (42 references)

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Moscow) and L. A. Monastyreva. *Vop Virus* 16(4):475-  
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- 1221        TUMORAL SPLENOMEGALY. (Fr.) Raybaud, Cl.  
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- 1224        LETHAL MIDLINE GRANULOMA: A REVIEW OF THE  
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*Mountain Med J* 68(10):40-45, 1971. (44 references)
- 1225        THE PILL, THE SMEAR, AND CANCER. (E.)  
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N. Y.) and A. S. Powell. *New York J Med* 71(21):  
2513-2517, 1971. (15 references)
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- 1227        THE EPIDEMIOLOGY, ETIOLOGICAL FACTORS AND  
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- 1228        CHORIOCARCINOMA: INTRODUCTION: HISTOCOM-  
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(E.) Lawler, S. D. (Royal Marsden Hosp., London,  
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- 1231        MACROPHAGES AND DELAYED-TYPE HYPERSENSI-  
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Med., Bronx, N. Y.) and B. Bennett. *Seminars Hemat*  
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- 1232        TOBACCO CHEWING IN ENGLISH COAL MINERS: A  
              PRELIMINARY REPORT. (E.) Tyldesley, W. R.  
(Dept. Dental Surg., U. Liverpool, England). *Brit J*  
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- 1233        HIGH RISK GROUPS IN COLON AND RECTUM NEO-  
              PLASIA. (Ger.) Oppolzer, R. (No affili-  
ation). *Osterr Zschr Krebsforsch* 26(5):341-348, 1971.  
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*Zschr Krebsforsch* 26(5):361-371, 1971. (No references)
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              CANCE OF HIGH RISK GROUPS. (Ger.) Holzner  
H. (No affiliation). *Osterr Zschr Krebsforsch* 26(5):  
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- 1237        NEOPLASTIC DISEASES OF THE UROGENITAL AP-  
              PARATUS. (Ger.) Gasser, G. (No affilia-  
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- 1239        THE INDIVIDUAL CANCER HAZARD FOR THE PRAC-  
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- 1240        SOME DATA ON PRIMARY MALIGNANT DOUBLE TUMOR  
              (RECORDED BY THE UNIVERSITY CANCER CENTER  
OF UTRECHT BETWEEN 1953-1970). (Dut.) Koster, L.  
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*Tidj Geneeskunde* 115(45):1882-1886, 1971. (20 ref-  
erences)



## CHEMICAL CARCINOGENESIS

### ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MAMMALIAN LIVER CELL CULTURE: II. EFFECTS OF ACTINOMYCIN D AND CYCLOHEXIMIDE ON INDUCTION PROPERTIES BY PHENOBARBITAL OR POLYCYCLIC HYDROCARBONS.

Nebert, D. W. (Nat'l. Inst. Child Hlth., Bethesda, Md.) and J. E. Gielen. *J Biol Chem* 246(17):5206, 1971.

Effects of actinomycin D and cycloheximide on the induction of aryl hydrocarbon hydroxylase in fetal rat hepatocyte cultures by benz[a]anthracene (BA) and by phenobarbital (PB) are reported. Actinomycin D decreased accumulation of the enzyme by 30% in cells treated with PB, whereas the accumulation of enzyme in A-treated cells was not appreciably affected. Cycloheximide inhibited enzyme activity by more than 50% in PB-treated cells, while induction in BA-treated cells was not affected. Neither actinomycin D nor cycloheximide acted by increasing enzyme degradation. Actinomycin D may even stabilize the enzyme. Actinomycin D did not prevent induction of enzyme if cells had been previously treated with cycloheximide and then with PB or BA. It was concluded that enzyme induction required initial RNA and protein synthesis followed by continued protein synthesis. The primary action of PB and BA may have been at the level of transcription with a secondary, lesser effect on enzyme degradation.

### COMPARISON OF MACROMOLECULAR BINDING OF ESTRADIOL IN HORMONE-DEPENDENT AND HORMONE-INDEPENDENT RAT MAMMARY CARCINOMA. (E.) McGuire, W. J. (Texas Med. Sch., San Antonio) and J. A. Julian. *Cancer Res* 31(10):1440-1445, 1971.

Characterization and Sephadex G-100 chromatographic analysis of tumors from rats given labeled  $17\beta$ -estradiol showed that most of the estradiol bound to hormone-dependent tumors was not retained by the Sephadex column. No significant binding of estradiol to hormone-independent tumors occurred. Estradiol-containing peaks were isolated from hormone-dependent tumor extracts centrifuged on sucrose gradients. The 8S component was found only in hormone-dependent tumors whereas the 4S binding was found in both hormone-dependent and -independent tumors. The 4S site of hormone-dependent tumors was specific for estradiol but the 4S site of hormone-independent tumors was nonspecific as determined by competitive binding and estradiol binding kinetics. Specific estradiol binding also was found only in hormone-dependent tumors.

### INHIBITION OF SPONTANEOUS DEVELOPMENT OF HYPERPLASTIC ALVEOLAR NODULES AND MAMMARY TUMORS IN C3H MICE FED PHENYLALANINE-DEFICIENT DIETS. (E.) Hui, Y. H. (Dept. Nutr. Sci., U. California, Berkeley), K. B. DeOme and G. M. Briggs. *J Nat Cancer Inst* 47(3):687-695, 1971.

Effect of a phenylalanine (P)-deficient diet was studied both on spontaneous hyperplastic alveolar nod-

ules (HAN) development and on tumorigenesis in virgin C3H/Crgl female mice. Over a 20 mo. period, mice fed diets with 0.075 and 0.090% P failed to develop nodules or tumors. Mice fed diets containing 0.135, 0.150 and 0.300% P had a 100% incidence of nodules at the end of 10 mo. and 85, 89 and 100% incidences of mammary tumors, respectively, after 20 mo. Mice fed a diet with an intermediate level of 0.120% P had a 32% incidence of nodules and a 24% incidence of tumor development at the end of 20 mo. Mice, pair-weighted with the 0.120% P group by receiving restricted amounts of the 0.300% P diet so that their body wt closely equaled those mice fed 0.120% P, showed a 70% incidence of nodules and 30% tumor formation at the end of 20 mo. This incidence of high nodule and low tumor development in pair-weighted controls suggests the presence of a specific effect of a P-deficient diet in spontaneous mammary-gland tumor development unaccounted for by partial starvation.

### 1244 REDUCTION AND ENHANCEMENT BY PHENOBARBITAL OF HEPATOCARCINOGENESIS INDUCED IN THE RAT BY 2-ACETYLAMINOFLUORENE. (E.) Peraino, C. (Argonne Natl. Lab., Ill.), R. J. M. Fry and E. Staffeldt. *Cancer Res* 31(10):1506-1512, 1971.

The simultaneous feeding of the carcinogen, 2-acetylaminofluorene (AAF; 0.01 or 0.02%) and phenobarbital (PB; 0.05%) reduced the incidence of hepatomas from that induced by AAF alone in 22-day old male rats. Rats fed a diet containing AAF for 20 to 90 days and then returned to a diet containing PB showed an increase in the incidence of hepatomas compared to rats fed a control diet after the AAF treatment. Both the duration of feeding of AAF and the feeding of PB affected the incidence of tumors. The enhancing effect of PB decreased as the period of AAF feeding was increased. Studies on the effects of AAF, PB and simultaneous AAF-PB showed that AAF had a long-term effect on stimulation of hepatocytes and that PB was able to reduce this effect if given simultaneously. PB also could produce a short-lived stimulation of hepatocyte proliferation.

### 1245 EFFECTS OF PHORBOL AND FOUR DIESTERS OF PHORBOL ON THE INCORPORATION OF TRITIATED PRECURSORS INTO DNA, RNA, AND PROTEIN IN MOUSE EPIDERMIS. (E.) Baird, W. M. (McArdle Lab. Cancer Res., U. Wisconsin Med. Ctr., Madison), J. A. Sedgwick and R. K. Boutwell. *Cancer Res* 31(10):1434-1439, 1971.

The incorporation of  $^3\text{H}$ -thymidine,  $^3\text{H}$ -cytidine and  $^3\text{H}$ -L-leucine into macromolecules of female STS mouse epidermal cells was observed after painting the skin with equimolar quantities of phorbol or one of four phorbol diesters. Incorporation of all labels was stimulated to varying degrees in relation to the tumor promoting activity of the phorbol ester. Epidermal inflammation and hyperplasia was also proportional to the tumor promoting activity, being almost nonexistent for phorbol and phorbol-12,13-diacetate, slight for phorbol-12,13-dibenzoate, moderate for phorbol-12,13-didecanoate, and marked in the case of 12-O-tetradecanoyl-phorbol-13-acetate.

- 1246 MORPHOLOGIC DIFFERENTIATION OF MOUSE NEUROBLASTOMA CELLS INDUCED *IN VITRO* BY DIBUTYRYL ADENOSINE 3':5'-CYCLIC MONOPHOSPHATE. (E.) Prasad, K. N. (U. Colorado Med. Ctr., Denver) and A. W. Hsie. *Nature* 233(39):141-142, 1971.

Mouse neuroblastoma cells, the neuronal nature of which was indicated by the fact that acetylcholinesterase but not butylcholinesterase was produced, were treated with N<sup>6</sup>O<sup>2</sup>-dibutyladenosine 3':5'-cyclic monophosphate (dibutyladenosine 3':5'-cyclic AMP). The cells were examined and stained at various time intervals. The formation of axons (cytoplasmic extension > 50 µm) was taken as an index of differentiation, while enlargement of cells and cell nuclei, and appearance of granular cytoplasm after differentiation were seen as a manifestation of maturation. Gross observation of living and stained cells showed that dibutyladenosine 3':5'-cyclic AMP induced axon formation as early as 24 hr after the addition of dibutyladenosine 3':5'-cyclic AMP; the maximum number of cells with axons, however, was seen 3-5 days after the addition of this compound. Further experimentation showed that the differentiation induced by dibutyladenosine 3':5'-cyclic AMP was, for the most part, irreversible and that the growth rate, but not the morphological changes, were a function of the dibutyladenosine 3':5'-cyclic AMP concentration used. Results indicated that the metabolic changes necessary for the expression of differentiated phenotype require at least one generation time. This is in contrast to the dibutyladenosine 3':5'-cyclic AMP-induced morphological transformation of Chinese hamster ovary cells and fibroblasts which occur in a period much shorter than a generation time. The maximum number of differentiated cells is present three to four days after the addition of dibutyladenosine 3':5'-cyclic AMP. It is suggested that interaction between these cells and the surface of the culture flask may be important, since flask surface has been shown to play a role in directing the synthesis of macromolecules in the differentiation of neuroblastoma cells induced by bromodeoxyuridine.

- 1247 THE ROLE OF N-OXIDATION PRODUCTS OF AROMATIC AMINES IN THE INDUCTION OF BLADDER CANCER IN THE DOG. (E.) Radomski, J. L. (U. Miami Sch. Med., Fla.) and E. Brill. *Arch Toxicol* 28(5):159-175, 1971.

Gas chromatography was used to quantitate N-hydroxy and nitroso oxidation products of 1- and 2-naphthylamine (1-NA and 2-NA) in urine of dogs given a single p.o. dose. The possible role of these oxidation products in the induction of bladder cancer is discussed. Dogs given 70 mg/kg of either 1-NA or 2-NA excreted the same amounts of oxidation products. Administration of 5 mg/kg 2-NA resulted in excretion of 0.2% of the dose whereas only trace amounts of the N-oxidation products of the same dose of 1-NA were detected. Using blood methemoglobin production as a measure of the amount of N-hydroxylation occurring, it was found that 70 mg/kg 2-NA administration produced more N-oxidation products than the same amount of 1-NA. Administration of 4-aminobiphenyl (4-ABP), a more po-

tent carcinogen than either 1-NA or 2-NA, resulted in urine N-oxidation products and blood methemoglobin levels which were higher than those seen with 2-NA. It is suggested that the formation of N-oxidation products may play an etiological role in production of bladder cancer by 2-NA and 4-ABP.

- 1248 CARCINOGENICITY TESTING OF N-HYDROXY AND OTHER OXIDATION AND DECOMPOSITION PRODUCTS OF 1- AND 2-NAPHTHYLAMINE. (E.) Radomski, J. L. (U. Miami, Sch. Med., Fla.), E. Brill, W. B. Deichmann and E. M. Glass. *Cancer Res* 31(10):1461-1467, 1971.

Carcinogenic abilities of N-hydroxy-2-naphthylamine (2-NOH), N-hydroxy-1-naphthylamine (1-NOH), 2-amino-1,4-naphthoquinone-N<sup>4</sup> (QA), 2-naphthylamine (2-NA) and dibenzo(a,h)phenazine (DBP) were studied in a variety of mammals. 46.7% of male rats and 41.7% of female rats given 1-NOH developed tumors (fibromas, granulomas, fibrosarcomas and hepatomas) whereas 2-NOH produced no tumors. Tests on newborn mice indicated that 2-NOH produced more tumors (62.5%) than did 1-NOH (22.9%). 1-NA, 2-NA, QA and DBP also were slightly carcinogenic in newborn mice. Direct application of 2-NOH to bladder mucosa of dogs by catheterization over a 30-month period resulted in papillary transitional cell carcinoma in 3 out of 4 cases. 2-NA produced no pathological changes in dog bladder. DBP administered p.o. for up to four years produced no bladder pathology either. QA and 2-NA both produced "precarcinogenic" changes in bladders of all dogs tested over a 41 month period. Studies comparing urine cytology and histological specimens from dogs indicated that the correlation between bladder pathology and the findings of abnormal cytology was poor.

- 1249 ULTRASTRUCTURAL AND BIOCHEMICAL STUDIES ON RIBONUCLEOPROTEIN PARTICLES FROM ISOLATED NUCLEOLI OF THIOACETAMIDE-TREATED RAT LIVER. (E.) Koshiba, K. (Baylor Coll. Med., Houston, Tex.), C. Thirumalachary, Y. Daskal and H. Busch. *Exp Cell Res* 68(2):235-246, 1971.

Nucleolar ribonucleoprotein (RNP) particles isolated from livers of male Holtzman rats after i.p. administration of 50 mg/kg body wt thioacetamide for eight days were centrifuged on sucrose density gradients. The three peaks recovered each contained 200-250 Å diameter spherical RNP particles which were composed of granules and filaments about 25 Å in diameter. These were thought to correspond to ribosomal subunits by virtue of their ultrastructural appearance which was the same as particles extracted from normal liver. The recovery of RNP particles from thioacetamide treated rat livers was, in this case, 30 times that recovered from normal liver. The most rapidly sedimenting RNP peak contained relatively more RNA relative to protein than did the other two peaks. These results differ from those of Liau et al. who found relatively more protein in the rapidly sedimenting fraction. 28S RNA was the predominant species of all three peaks and also of whole RNP particles.



- 1250 EFFECTS OF LONG-TERM ADMINISTRATION OF ESTROGEN ON THE OCCURRENCE OF MAMMARY CANCER IN WOMEN. (E.) Burch, J. C. (Vanderbilt U. Sch. Med., Nashville, Tenn.) and B. F. Byrd, Jr. *Ann Surg* 174(3):414-418, 1971.

The incidence of breast disease, general mortality and mortality due to cancer were studied in a group of 511 women, aged 27 to 72, who underwent hysterectomy and had estrogen treatment postoperatively. Forty-five of these patients developed benign breast tumors. An additional nine patients developed malignant breast tumors. The incidence of benign and malignant breast tumors was no greater than that expected for such a population. Mammary cancer did not appear in the study group until about age 50, which is ten years later than expected for the general population. There were no deaths due to mammary cancer during the study period. The observed mortality rate after age 45 in the estrogen-treated women was less than 50%, the expected rate in a comparable age group. After age 40, the experimental group showed a steady decrease in the incidence of malignant disease and the realized incidence of new malignant neoplasms never exceeded one-third of the expected values. It is concluded that long term administration of estrogens produces a very favorable decline in the real mortality rate.

- 251 INHIBITION OF HEPATIC MACROMOLECULE SYNTHESIS BY SINGLE DOSES OF *N*-HYDROXY-2-FLUORENYLACETAMIDE. (E.) Marsh, J. B. (Sch. Dental Med., U. Pennsylvania, Philadelphia) and D. L. Rabkin. *Biochem Pharmacol* 20(9):2205-2211, 1971.

Liver regeneration after partial hepatectomy and proteinuria by male rats with experimental nephrosis were found to be inhibited by a single i.p. injection of 40 mg/kg *N*-hydroxy-2-fluorenylacetamide. Male rats of the Holtzman strain weighing about 150 g were used. There was also inhibition of the incorporation of labeled precursors into hepatic RNA and DNA, with control rats showing no such inhibitory effects. Greater effects were seen on DNA labeling. The results suggest that *N*-hydroxy-2-fluorenylacetamide may affect regulatory mechanisms involved in cell division. The technique employed should prove of value in further exploration of the problem of induction of hepatic cell division and its reaction to chemical carcinogens.

- 252 ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MAMMALIAN LIVER CELL CULTURE: I. STIMULATION OF ENZYME ACTIVITY IN NONHEPATIC CELLS AND IN HEPATIC CELLS BY PHENOBARBITAL, POLYCYCLIC HYDROCARBONS, AND 2,2-BIS(*p*-CHLOROPHENYL)-1,1,1-TRICHLOROETHANE. (E.) Gielen, J. E. (Nat'l. Inst. Child Health, Bethesda, Md.) and D. W. Nebert. *J Biol Chem* 246(17):5189-5198, 1971.

phenobarbital (PB; 2.0 mM), 2,2-bis (*p*-chlorophenyl)-1,1,1-trichloroethane (*p,p'*-DDT; 100  $\mu$ M), benz[a]anthracene (BA; 13  $\mu$ M) and 3-methylcholanthrene (MC;

0-75  $\mu$ M) were found to induce aryl hydrocarbon hydroxylase activity in primary cultures of fetal rat hepatocytes and whole fetal rat embryos, as well as in chick, mouse, hamster and rabbit liver cells. The enzyme activity of all cells tested was stimulated more by the polycyclic hydrocarbon, BA, than by PB. The maximally inducible level of rat hepatocyte enzyme was about the same as that found in newborn rat liver and about half that of adult rats. Stimulation of the enzyme in cultured hepatocytes was maximal between the second and fourth day of culture. The time required for a doubling of oxygenase activity in hepatocytes treated with either PB or BA was about three hr. Enzyme levels declined after the fourth day. Although both PB and BA slightly decreased hepatocyte protein synthesis and BA reduced RNA synthesis by 30%, the mean generation time was not affected. PB plus BA, BA plus *p,p'*-DDT, MC plus PB and MC plus *p,p'*-DDT were additive in their ability to induce enzyme, whereas the level produced by PB plus *p,p'*-DDT was reduced. MC plus BA had no inductive effect. Enzyme activity declined in cells pretreated with PB or BA with a half-life of 10.5 hrs. After 24 hrs., the half-life slowed to 21 hrs., an effect thought to reflect the increase in dying hepatocytes.  $K_m$ s for constitutive, PB- and BA-induced hydroxylase were all similar in the presence of the substrate, benzo[a]pyrene.

- 1253 MUCOR DIVERGENCE IN AFLATOXIN EFFECTS WITH DUCKLING BILE AND PLASMA. (E.) Lynd, J. Q. (Agron. Dept., Oklahoma State U., Stillwater) and F. T. Lynd. *Environmental Res* 4:316-324, 1971.

The ability of *Mucor* extract (an aflatoxin antagonist) to inhibit or reverse liver, bile and plasma changes induced in newborn Hile Mammouth White Pekin ducklings fed a defined diet containing sublethal levels of aflatoxin was studied over a ten day period. Aflatoxin decreased the growth rate of ducklings. Liver size in relation to body weight increased in experimental animals whereas it decreased in the controls. Bile riboflavin content decreased about three-fold while controls showed an increase of about six-fold. Flavin monophosphate, total lipids and lipase activity of plasma were repressed by aflatoxin. Amendment of the aflatoxin-containing diet to include *Mucor* factor restored growth rate, liver size, bile riboflavin, plasma flavin monophosphate, total lipids and lipase to levels very close to those of the controls. Addition of riboflavin plus pantothenol to the diet partially restored some parameters when compared to addition of riboflavin alone. *Mucor* extract also produced near-normal hepatic cell development.

- 1254 THE RELATIONSHIP BETWEEN THE CHEMICAL STRUCTURE OF AFLATOXINS AND THEIR EFFECT ON BOVINE PANCREAS DEOXYRIBONUCLEASE. (E.) Schabort, J. C. (Dept. Nutr., Rand Afrikaans U., Johannesburg, South Africa) and M. J. Pitout. *Enzymologia* 41(4):201-216, 1971.

Aflatoxins B<sub>1</sub>, B<sub>2</sub>, and M<sub>2</sub>, at concentrations less

than 80  $\mu$ M, activated pancreatic deoxyribonuclease. This activity correlated with the ability to bind to DNA, as determined by differential spectroscopy. B<sub>1</sub> was the best activator, binding with strongest affinity to DNA (B<sub>1</sub>>B<sub>2</sub>>M<sub>2</sub>). B<sub>1</sub>, B<sub>2</sub> and M<sub>2</sub> decreased the apparent Michaelis constant for DNA in deoxyribonuclease assay, and thus increased the affinity of the nuclease for the DNA-aflatoxin complex. Aflatoxins B<sub>2</sub>a, G<sub>2</sub>a, G<sub>2</sub> and M<sub>1</sub> were noncompetitive inhibitors of the deoxyribonuclease, the degree of inhibition depending on the affinity of binding to the enzyme (B<sub>2</sub>a>G<sub>2</sub>a>M<sub>1</sub>). Aflatoxin G<sub>1</sub> did not affect enzyme activity. The pertinence of these results to carcinogenic activity of aflatoxins was discussed.

- 1255 A COMPARATIVE STUDY OF AFLATOXIN B<sub>1</sub> METABOLISM IN MICE AND RATS. (E.) Steyn, M. (South African Med. Res. Council, Pretoria), M. J. Pitout and I. F. H. Purchase. *Brit J Cancer* 25(2): 291-297, 1971.

A study of the difference between mice and rats in their ability to convert aflatoxin B<sub>1</sub> into fluorescent metabolites (designated x<sub>1</sub>, x<sub>2</sub>, and x<sub>3</sub>) is described in relation to the apparent resistance of the mouse to the carcinogenic effects of this toxin. *In vivo* experiments on the metabolism of aflatoxin B<sub>1</sub> revealed that only the mouse is able to metabolize the toxin to three fluorescent metabolites in addition to the known aflatoxin M<sub>1</sub>. The ability of the mouse to absorb consistently more aflatoxin B<sub>1</sub> from its stomach than the rat was clearly demonstrated. *In vitro* experiments showed that only the microsomal fraction of mouse liver is capable of producing a variety of fluorescent metabolites from aflatoxin B<sub>1</sub>, and that NADPH was needed as a co-factor. The absence of carcinogenicity of aflatoxin in mice may be related to the rapid metabolism. It is pointed out that the mouse can hydroxylate aflatoxin B<sub>1</sub> to aflatoxin M<sub>1</sub> and that the metabolites x<sub>1</sub>, x<sub>2</sub> and x<sub>3</sub> and aflatoxin M<sub>1</sub> were produced independently of each other.

- 1256 IRREVERSIBLE CHANGE OF THE PATTERN OF CARCINOGENIC AMINOAZO DYE-BINDING PROTEINS IN RAT LIVER DURING CONTINUOUS FEEDING OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE. (E.) Sugimoto, T. (Fac. Sci., U. Tokyo, Japan) and H. Terayama. *Cancer Res* 31(10):1478-1482, 1971.

The permanence of changes in 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), binding proteins isolated from heat-treated cell sap of rat hepatocytes was studied. Rats fed a dye-containing diet for either 2 wks. or one mo. and then maintained on a dye-free diet were given an intragastric dose of 40 mg 3'-Me-DAB. The dye-binding proteins were separated by carboxy-methylcellulose chromatography or Sephadex G-100 gel filtration into several fractions, with fractions I, IV, VI and VII containing the dye-protein complexes. The ratio of binding to two components of Fraction I, Ia and Ib, changed with continuous dye feeding and relatively more dye was bound to Ib. The subsequent 3'-Me-DAB-free period

did not alter the overall binding capacity of fraction I nor did the relative binding capacity of the components change. This suggests that the changes in binding of 3'-Me-DAB were permanent. Similar changes were noted in components IV-a, IV-b and IV-c of fraction IV. Controls had high binding in IV-a. With continuous dye feeding, however, binding to this component decreased and binding increased greatly in IV-c. Since permanent binding changes were seen in the acidic protein fractions I and IV, it was postulated that these changes may be involved in mechanisms of carcinogenesis.

- 1257 MORPHOLOGY AND GROWTH PATTERNS OF COLONIES OF LIVER CELL LINES DERIVED FROM RATS FED WITH 4-DIMETHYLAMINOAZOBENZENE. (E.) Chikata, E. (Okayama U. Med. Sch., Japan). *Acta Med Okayama* 24 (6):559-571, 1970.

Rats were fed various amounts of 4-dimethylaminoazobenzene (DAB) for 57, 107, 142, 191, and 312 days. A liver cell culture line was established at the end of each period and designated as dRLN-53, dRLN-60, dRLN-61, dRLa-74, and dRLh-84 according to the carcinogen dosage. Plating was done to initiate colony formations when the cultures were about one year old. It was discovered from the colony cells that cell morphology was controlled directly by the amount of carcinogen administered. Cells from rats given DAB for only 57 days had an almost normal appearance and few colonies, while cells from rats given DAB for 312 days had large cells (many of which were multinucleated) and large colonies exhibiting loss of contact inhibition. The other three cell lines fell in stepwise order between these two extremes. Measurement of plating efficiency showed that the values ranged from 24-40% in proportion to the amount of DAB administered; the size of the colony was also increased as the amount of DAB was increased. Atypism and pleomorphism were found to be directly related to both the size of the colony and the duration of DAB feeding. Due to an increase in migrating cells, it was found that the greater the dose of DAB, the more irregular the colony. It is concluded that the increase in percentage of colonies with atypism and pleomorphism of cells in proportion to DAB feeding duration is correlated with the higher incidence of abnormal mitosis in cancer cells.

- 1258 IMMUNOELECTROPHORETIC ANALYSIS OF DMBA-INDUCED RAT MAMMARY TUMOURS. (E.) Kellen, J. A. (Dept. Path. Chem., U. Toronto, Canada), A. C. -H. Lo, and T. O. Kolos. *Oncology* 25(5):401-409, 1971.

Antisera obtained from rabbits immunized with several rat mammary tumors induced by 7,12-dimethylbenz(a)-anthracene (DMBA) were absorbed with normal rat serum and organ lyophilizates and analyzed using immunoelectrophoresis. DMBA-induced tumors of varying histologic types produced precipitation bands when absorbed with rabbit antiserum from immunization with one rat mammary adenocarcinoma. The number of bands



varied from two to five; however, all showed a distinct band in the  $\beta$ -region which is not transferrin. The bands represent antigens with mobility in the  $\alpha$ - and  $\beta$ -serum-globulin region. Some weak  $\alpha$ -globulin lines were also seen. The characteristic  $\beta$ -region line was not seen when normal or hypertrophic mammary glands were used.  $\alpha$ -Globulin lines varied according to the type of tumor.

- 259 INHIBITION OF CARCINOGENESIS BY DIETARY ZINC. (E.) Poswillo, D. E. (Royal Coll. Surg. of England, London) and B. Cohen. *Nature* 231 (5003):447-448, 1971.

Forty young Syrian golden hamsters were divided into three groups of 10, 10 and 20 animals, resp., matched for size and sex. All animals were maintained on a pellet diet which contained 21.9 ppm of zinc. One group received 21.9 ppm of zinc sulphate in the drinking water. Ten animals in the second group were subjected to a standardized injury in the right cheek pouch by means of electrocautery. Four days later and three times weekly for the next four weeks, the right cheek pouch of each animal was painted with a solution of dimethylbenzanthracene (DMBA) in liquid paraffin. The administration of zinc as a dietary supplement appeared to exert an inhibitory effect on tumor formation. Animals which had not received the zinc supplement but whose pouches had been injured were less protected against the effect of DMBA but markedly less susceptible than the control group. It appeared that some protection had been afforded at the site of application of the carcinogen, in view of the localization of zinc at the site of an injury. After ten months of observation, there was no increase in tumor formation in the animals receiving zinc solution.

- 260 THE METABOLISM OF 7,12-DIMETHYLBENZ(a)ANTHRACENE BY HOMOGENATES OF THE STOMACH AND SMALL INTESTINE OF MICE. (E.) Gentil, A. (Chester Beatty Res. Inst., London, England) and P. Sims. *Z Krebsforsch* 76(3):223-230, 1971.

The formation of 7,12-dimethylbenz(a)anthracene (DMBA) metabolites was studied in homogenates of forestomachs, glandular stomachs and intestine of control mice and mice pretreated with 3-methylcholanthrene (3-MC), in order to determine whether DMBA, alone or together with its metabolites, is responsible for inducing murine gastric and intestinal tumors. 3-MC induced the production of "aryl hydrocarbon hydroxylase", an enzyme involved in the metabolism of DMBA. Isotopically labeled metabolites were identified by thin-layer chromatography. Observed levels of oxidation products of DMBA in stomach and intestine homogenates were generally lower than those previously reported in rat liver. Pretreatment of mice by administration of 3-MC p.o. resulted in a 15-fold increase in aryl hydrocarbon hydroxylase activity. The possible role of oxidation products of DMBA in inducing stomach, intestine and mesenteric tumors is discussed in relation to current literature.

- 1261 ISOLATION OF *IN VIVO* INTERACTION COMPOUNDS OF POLYCYCLIC HYDROCARBONS WITH NUCLEIC ACIDS AND PROTEINS. (E.) Prodi, G. (Inst. Gen. Path., U. Bologna, Italy), S. Grilli, P. Rocchi and A. M. Ferreri. *Arch Sci Biol* 54:129-140, 1970.

Isolation methods were devised to define the nature of the reaction which occurs between an oncogenic substance and the substratum, and therefore to define the type of carcinogenic action of polycyclic hydrocarbons. The substratum used in this study was nucleic acid of the liver, lung and spleen of [ $^3\text{H}$ ] dimethylbenzanthracene (DMBA)- or [ $^3\text{H}$ ] benzo(a)pyrene (BP)-i.p. injected female Wistar rats. Animals were sacrificed 22 hrs after injection. The organs were extracted to yield four fractions: DNA or RNA, nuclear proteins and cytoplasmic proteins. The nucleic acid fractions were hydrolyzed to pyrimidine nucleotides and purine bases. These radioactive compounds were then subjected to three methods of isolation: column chromatography, electrophoresis and paper chromatography. Best results were obtained by gel filtration on Sephadex G10, which yielded radioactive compounds whose ultraviolet absorption did not correspond to that for DMBA or BP and may be mononucleotides bearing polycyclic groups. Most of the radioactivity was found to be tritiated water. Two hypotheses were proposed: the polycyclic hydrocarbon reacts with the substratum after a metabolic transformation and becomes detached from it immediately after the reaction, leaving an active part of the molecule; or the aromatic compound remains attached to a long chain of polynucleotides or polypeptides giving a highly polar character to the whole.

- 1262 STRAIN DISTRIBUTION AND LINKAGE TESTS OF 7,12-DIMETHYLBENZANTHRACENE (DMBA) INFLAMMATORY RESPONSE IN MICE. (E.) Taylor, B. A. (Jackson Lab., Bar Harbor, Me.). *Life Sci* 10(19):1127-1134, 1971.

The effects of a single topical application of 7,12-dimethylbenzanthracene (DMBA) on 32 inbred and 21 congenic strains of mice are reported. Of the 32 inbred strains, mice of 23 strains developed ulcers at the site of application. Sensitivity to DMBA was apparently determined by the *In* locus. Development of papillomas subsequent to ulceration was associated only with *In* carrying strains, especially the two C3H lines tested. Results obtained with the 21 congenic strains indicated that the *In* locus was not closely linked to any of the 19 independent markers studied. The *In* locus, therefore, has not been located. Size and intensity of ulceration in six chimeric mice produced by fusion of embryos of two strains, one carrying an albino gene and the other the *nonagouti* gene, correlated well with coat color. White mice react mildly to DMBA. It seems likely that individual cells respond independently to the chemical according to their own genotype, and that the pigment cell population is a good indicator of the proportion of sensitive and insensitive cells.

- 1263 PARTIAL FRACTIONATION OF OESTRADIOL-BINDING CHROMATIN FROM DIMETHYLBENZANTHRACENE-INDUCED RAT MAMMARY TUMOR. (E.) Pooley, A. S. (Imperial Cancer Res. Fund, London, England) and R. J. B. King. *J Endocr* 51(2):231-240, 1971.

The possibility of a preferential binding of isotopically labeled estradiol-17 $\beta$  to chromatin from dimethylbenzanthracene induced rat mammary adenocarcinoma was studied by differential centrifugation of sonicated nuclei. The purification procedure resulted in dispersion of the heterochromatin in practically all nuclei so that the subsequent fractionation of chromatin by centrifugation was probably not due to the presence of heterochromatin. More estradiol was associated with the "light" chromatin which sedimented at a high centrifugal force. The estradiol-bound fractions also appeared to have the greatest template activity. It is concluded that preferential binding of estradiol does exist.

- 1264 IDENTITY OF CORTICOSTEROID BINDER I WITH THE MACROMOLECULE BINDING 3-METHYLCHOLANTHRENE IN LIVER CYTOSOL *IN VIVO*. (E.) Singer, S. (Temple U. Sch. Med., Philadelphia, Pa.) and G. Litwack. *Cancer Res* 31(10):1364-1368, 1971.

"Corticosteroid Binder I" has been shown to be identical to the protein which is able to bind the carcinogen, 3-methylcholanthrene (MC), in rat liver. When binder I was purified from hepatocytes of rats simultaneously labeled with  $^{14}\text{C}$ -MC and  $^3\text{H}$ -cortisol, both labels were recovered. Cortisol- and MC-binding proteins, purified on Sephadex G-75 columns, showed the same migration pattern when subjected to isoelectrofocusing. Purified MC-binding protein also bound labeled corticosterone. The molecular weights of the two protein-bound complexes were the same, approximately 38,000, and agreed with values previously reported.

- 1265 INDUCTION OF SQUAMOUS CELL CARCINOMA IN THE RESPIRATORY TRACT OF MICE. (E.) Nettesheim, P. (Oak Ridge Natl. Lab., Tenn.) and A. S. Hammons. *J Nat Cancer Inst* 47(3):697-701, 1971.

Mice of specific pathogen-free strains (C57BL x C3H)-F<sub>1</sub> (BC3F<sub>1</sub>), and DBA/2 males, 10 to 12 weeks old, were given six and four, resp., weekly injections of 3-methylcholanthrene (MCA) in order to study the induction of squamous cell carcinomas in the respiratory tract. Three of 50 DBA/2 mice developed squamous cell carcinomas after receiving four weekly injections of 0.5 mg MCA with an induction period of seven months. In BC3F<sub>1</sub> mice given six weekly injections of the same dose of MCA, 86% showed tumors after an induction time of 10-28 weeks. These tumors showed frank invasion and metastasis and were found to be readily transplantable to isogenic recipients. The first metaplastic lesions seem to develop in the peripheral bronchioli and alveolar portions of the lung. However, massive squamous cell metaplasia and squamous cell carcinoma involving large airways were regularly observed at later stages. It is not as yet determined

if primary bronchogenic carcinoma or bronchiolo-alveolar carcinoma with secondary invasion of primary bronchi in these mice have been induced. Results indicate that it would be feasible to use the mouse as an experimental animal for further respiratory carcinogenesis studies.

- 1266 MORPHOGENESIS OF EPITHELIAL NEOPLASMS INDUCED IN THE RAT KIDNEY BY DIMETHYLNITROSAMINE. (E.) Hard, G. C. (Med. Res. Council Lab., Carshalton, England) and W. H. Butler. *Cancer Res* 31(10):1496-1505, 1971.

Doses of 30 mg/kg body wt dimethylnitrosamine (DMN) caused the formation of lipid droplets and "cytoseg-resomes" in cells of the proximal convoluted tubules of the rat kidney within 24 hr. By three to four days cell debris accumulated beneath the epithelial cells at the basement membrane and the apical microvilli of the cells were lost. Monocytic infiltration began about the fourth day and the inflammatory reaction reached a peak by about seven days. Many cells were then necrotic. Regeneration of tubular epithelium had begun by this time and dividing cells were seen until total regeneration, which took two to three wk. three wk, nuclei of tubular cells were seen to enlarge and by six wk many were bizarrely shaped. These late changes were observed in all three sections of the convoluted tubules. Invasive neoplasms developed in some cases by three months. The neoplastic cells exhibited abnormal brush borders and abnormal nucleoli and were classed as adenocarcinoma. Higher doses of DMN (50 to 60 mg/kg body wt.) produced the initial effects extended to all sections of the convoluted tubules.

- 1267 LIVER CARCINOMAS INDUCED IN RATS BY SINGLE ADMINISTRATION OF DIMETHYLNITROSAMINE AFTER PARTIAL HEPATECTOMY. (E.) Craddock, V. M. (Med. Res. Council Labs., Carshalton, Surrey, England). *J Nat Cancer Inst* 47(4):899-907, 1971.

Female albino rats of the Porton strain 9 to 10 weeks of age, had either hepatectomy of the median and left lateral lobes or sham operations. The rats were then injected i.p. at various times with dimethylnitrosamine (DMN), a liver carcinogen, to determine whether an event during cell replication might be the critical point of carcinogenic action. First, the rate of metabolism of DMN was determined in both control and hepatectomized groups by  $^{14}\text{C}$ -DMN measurement of exhaled  $^{14}\text{C}$ -CO<sub>2</sub>. Metabolism was found to be delayed for three hours in both groups, presumably the result of surgical stress; at 6 hr post-surgery, metabolic breakdown of DMN had returned to normal except at the time of DNA replication (24 hours) and of mitosis (30 hours). At these two periods metabolism was slowed. Both groups of rats were then analyzed over a two-year period for their reaction to the carcinogen, with all rats injected with DMN developing liver sarcomas, trabecular tumors, hyperplastic hemorrhagic liver nodules, and/or hemorrhagic



ic liver cells; lymphosarcomas and kidney tumors were also found in some cases. Experiments were performed in which dimethylformamide, a compound known to decrease the rate of DMN metabolism, was administered before DMN to determine if the effect of partial hepatectomy was due to the resultant slowing of the rate of DMN metabolism. None of the animals so treated developed liver nodules or liver tumors, demonstrating that tumors obtained after partial hepatectomy were not due to slowing the DMN metabolic rate. It was also found that all rats undergoing partial hepatectomy with no further treatments recovered and had normal liver surfaces. It is postulated that the methylation products affect the DNA since DMN is metabolized.

1268 KARYOTYPE ABERRATIONS OBSERVED *IN VITRO* IN CLONES OF N-METHYLNITROSO-UREA-INDUCED POLYPOID SARCOMA OF THE RAT SPINAL CORD. (Ger.) Thust, H. (Acad. Med., Erfurt, Germany). *Exp Path* 5:226-234, 1971.

Chromosomal studies performed on an intramedullary sarcoma, which had been induced by i.v. administration of N-methyl-nitrosourea (MNU) to a Hauben male rat (25 mg/kg at four wk intervals) after a latency period of 317 days, are described. The tumor was transplanted intracerebrally and explanted upon development 26 days later; it was preserved in medium at -78° C following trypsinization. Ninety-four days later another implant of the tumor was made to female rat receivers; one portion of the explant was cultured in Bucher flasks and another portion was used for nine *in vivo* passages to female rat receivers. *In vitro* cultivation techniques were applied and cloning was carried out on irradiated mononuclear rat brain feeder layers. Mitoses (30-60 per culture) were studied on processed samples. Up to ten karyotype analyses per sample indicated a structural deviation from the norm. The frequency distribution of chromosome figures per mitosis showed 42 chromosomes per mitosis in almost all cultures. Most clones showed the absence of single chromosomes and the presence of a specific chromosome marker; it was assumed that this occurred by centric fusion mechanisms during the reproduction stage preceding the second clonal stage. A distinct tendency towards tetraploidy was observed following long term clonal culture maintenance. The maintenance of normal chromosomal sets in this chemically-induced tumor constitutes a special case, and its relationship to DNA synthesis will constitute the subject of further autoradiographic studies.

1269 CARCINOGENESIS IN TISSUE CULTURE: XV. AGGREGATE-FORMING CAPACITY OF RAT LIVER CELLS. COMPARISON OF UNTREATED CONTROLS, CELLS TRANSFORMED IN CULTURE, AND TUMOR PRODUCED BY BACK-TRANSPLANTATION. (E.) Namba, M. (Okayama U. Med. Sch., Japan) and J. Sato. *Japan J Exp Med* 41(3): 233-245, 1971.

rat liver cells which were transformed by 4-nitro-2,3-dihydro-1H-benzoxazole 1-oxide (4NQO), 4-dimethylaminoazobenzene

(DAB) and 3'-methyl-4-dimethylaminoazobenzene as well as cells spontaneously transformed were studied for their ability to aggregate in roller cultures. The chemically transformed cells formed large, rough-surfaced aggregates whereas aggregates of control cells were small and spherical. The histological appearance of these aggregates resembled the aggregates of ascites tumor produced when these same transformed lines were backtransplanted into rats. It is concluded that the degree of aggregation of cells in tissue culture was a useful indicator of tumorigenic ability. Study of 4NQO transformation indicated that a transition period was necessary before the appearance of aggregability changes.

1270 ADENOCARCINOMA OF ETHMOIDS IN FURNITURE WORKERS. (E.) Hadfield, E. H. (Gen. Hosp., High Wycombe, England) and R. G. Macbeth. *Ann Otol* 80(5):699-703, 1971.

In the United Kingdom, incidence of adenocarcinoma of the ethmoids in males aged 15-64 years is .0006 per 1,000 of population. In male workers of the furniture industry in High Wycombe and environs, the rate is 0.7 per 1,000. A possible correlation between the disease and the occupation was noted. The disease occurs in men working or having worked in conditions exposing them to fine hard-wood dust. The disease originates in the anterior ethmoidal area and spreads only secondarily to the maxillary sinus. A nose survey of workers in the industry was made from June 1969 to June 1970. While office workers' noses were normal, the wood-workers very commonly showed a deposit of dust on the septum, and particularly at the anterior ends of the middle turbinates. Only one malignancy was found in the first year's survey. Two conclusions were indicated: 1) those workers with long-term exposure to the dusts show an increased squamous metaplasia in the smears; and 2) simple polypoidosis, common in these people, does not seem to lead to malignant change. Smears taken from the anterior end of the middle turbinate area, the area of maximal deposition of dust, showed a high proportion of squamous metaplasia, and usually many pus cells. The disease is thought to be an adenocarcinoma because: 1) the mucosa of the middle turbinate has many mucous glands (whereas the antral mucosa has not); 2) the squamous metaplasia permits a fine dust to be deposited which is not carried away by ciliary action and may get into the mucous glands in solid form or in solution; 3) and adenocarcinoma is a slowly-growing indolent condition which may be a result of a long-continued minor irritant.

1271 TOXICOLOGY AND CARCINOGENESIS OF VARIOUS CHEMICALS USED IN THE PREPARATION OF VACCINES. (E.) Mason, M. M. (Mason Res. Inst., Worcester, Mass.), C. C. Cate and J. Baker. *Clin Toxicol* 4(2):185-204, 1971.

This study was performed to determine the toxic and carcinogenic potential of seven compounds commonly used as preservatives or extracting agents in the preparation of commercially available biologics.

The compounds were: merthiolate, (Thimerosal), benzethonium chloride, methyl paraben, phenol red, pyridine, ethylene glycol, and ethylene chlorohydrin. Fischer 344 weanling rats of both sexes were used. Acute toxicity determinations and an approximation of LD<sub>50</sub> for each compound were performed. The supplementary study involved a four-week injection period with five dose levels to determine the maximum tolerated dose. A long term (one year) twice weekly s.c. inoculation series was maintained at four dose levels with careful evaluation of the incidence of tumors for the chronic study. Three major criteria were considered for assaying toxicity: survival time, weight gains, and drug-related organ pathology. It was found that Thimerosal had a high induction rate of bronchopneumonia, with concomitant lung lesions, as well as a high retardation rate for weight gain. Although the compound did cause the second highest number of fibromas, there was a dose-related inhibition of spontaneous interstitial cell tumors in Thimerosal animals. Benzethonium chloride caused the most retardation in weight gain and gave the most (26) injection-site-related fibrosarcomas in 200 treated animals (13%). All other compounds were well tolerated. Females were found to be highly susceptible to leukemias and pituitary adenomas, while males had a high incidence of adrenal tumors. Mammary fibroadenomas (some of which may be related to methyl paraben application), uterine polyps, and testicular tumors also occurred.

- 1272 CIGARETTE SMOKING AND CANCER OF THE MOUTH, PHARYNX, AND LARYNX: A CONTINUING STUDY. (E.) Moore, C. (U. Louisville Sch. Med., Ky.). *JAMA* 218(4):553-558, 1971.

This is the second part of a long term study concerning the effects of continued smoking on the recurrence of laryngeal, pharyngeal and oral cancers; the death risk of patients with a three to eighteen year history of control of such cancers was also examined. The 203 patients with histories of smoking were divided into two groups, one which continued to smoke and one which did not. All patients were followed for seven years. Of the patients who continued to smoke, 40% acquired second cancers in tissues exposed to tobacco smoke. Only 6% of ex-smokers acquired second cancers. The death rate in patients who continued to smoke was twice that of the ex-smokers. The death rate increased sharply after four or five years in the smoking population. That of the ex-smokers showed a random pattern. These results support previous evidence implicating the use of tobacco in the origin of cancers of the mouth and throat and showing that cessation of smoking is associated with a reduced risk of second cancers.

- 1273 SMOKING RISKS OF DIFFERENT TOBACCOS. (E.) Passey, R. D. (Chester Beatty Res. Inst., London, England), M. Blackmore, D. Warbrick-Smith and R. Jones. *Brit Med J* 4(5781):198-201, 1971.

Groups of white male rats were exposed for various

lengths of time to English cigarette and cigar smoke to determine what factors might influence lung lesion formation in human smokers. It was found that animals exposed to cigarette smoke for periods up to 60 days exhibited diseased and damaged tracheas, bronchi, and lungs. The tracheas and bronchi contained an excess of secretions and purulent cellular exudates; the linings of these organs were frequently hyperplastic. In advanced cases, the epithelial layers were damaged and disorganized with enlarged and inflamed mucous glands. On the other hand, rats exposed to cigar smoke for periods up to 251 days presented almost normal tissues and organs. The epithelial linings of the tracheas were not inflamed, although there were increases in goblet cell numbers. Also, there were no cellular exudates in the tracheas or bronchi and there were no instances of hyperplasia. The reason for these results lies primarily in the tobacco used in the study. Flue-cured cigarette tobacco has a high sugar content, an acid pH, and a high level of tar whereas air-cured cigar tobacco has a low sugar content, an alkaline pH, and a high level of nicotine. However, precisely which factor or factors might be involved was not indicated by experimental procedures used.

- 1274 ACUTE AND CHRONIC TOXICITY OF FURYLURAMIDE IN RATS AND MICE. (E.) Miyaji, T. (Osaka U. Med. Sch., Japan). *Tohoku J Exp Med* 103(4):331-36, 1971.

- 1275 HYPERGLYCEMIA PRODUCED BY ETHYLURETHAN IN THE RAT. (Fr.) Vaille, C. (Bichat Hosp., Paris, France), C. Debray, C. Roze and M. Souchard. *Ann Pharmaceut Fran* 29(9-10):477-483, 1971.

- 1276 AFLATOXINS IN AUTOPSY SPECIMENS FROM THAI CHILDREN WITH AN ACUTE DISEASE OF UNKNOWN AETIOLOGY. (E.) Shank, R. C. (Dept. Nutrition Food Sci., Massachusetts Inst. Tech., Cambridge), C. H. Bourgeois, N. Keschmaras and P. Chandavimol. *Fd Cosmet Toxicol* 9(4):501-507, 1971.

- 1277 HIGH AFLATOXIN PRODUCTION ON A CHEMICALLY DEFINED MEDIUM. (E.) Reddy, T. V. (Val-labhbhai Patel Chest Inst., U. Delhi, India), L. Viswanathan and T. A. Venkatasubramanian. *Appl Microbiol* 22(3):393-396, 1971.

- 1278 MUTAGENIC AND PROPHAGE-INDUCING ACTIVITIES OF 1-ALKYL-3-NITRO-1-NITROSOGUANIDINES. (E.) Iwahara, S. (Nat'l. Inst. Hyg. Sci., Tokyo, Japan), K. Yanagimachi, S. Kamiya, M. Nakadate and I. Suzuki. *Chem Pharm Bull* 19(9):1914-1918, 1971.

- 1279 BILIRUBIN GLUCURONIDATION BY HEPATIC MICROSOMAL SUBFRACTIONS AND THE EFFECT OF 3-METHYLCOLANTHRENE. (E.) Potrepka, R. F. (Coll. Med., U. Iowa, Iowa City) and J. L. Spratt. *Biochem Pharmacol* 20(9):2247-2252, 1971.



- 80 EFFECTS OF THE CARCINOGEN METHYLAZOXYMETHANOL ACETATE ON PROTEIN SYNTHESIS AND DRUG METABOLISM IN RAT LIVERS. (E.) Lundeen, P. B. (Dept. Oral Biol. Pharmacol., U. Michigan, Ann Arbor), G. S. Banks and R. W. Ruddon. *Biochem Pharmacol* 20(9):2522-2527, 1971.
- 81 MODIFICATION OF CATECHOLAMINE CONTENT OF MALE ACCESSORY SEXUAL TISSUES OF GUINEA PIG AFTER PRETREATMENT WITH MICROSOMAL ENZYME INHIBITORS. (E.) Cloutier, G. (Fac. Med., U. Montreal, Quebec, Canada) and A. L. Gascon. *Biochem Pharmacol* 20(9):2319-2325, 1971.
- 82 CYTOMORPHOLOGICAL CHANGES OF CULTURED CELLS FROM RAT LIVER, KIDNEY AND LUNG INDUCED BY SEVERAL MYCOTOXINS. (E.) Umeda, M. (Yokohama City Univ. Sch. Med., Japan). *Jap J Exp Med* 41(3):195-207, 1971.
- 83 INFLUENCE OF 3-METHYLCHOLANTHRENE AND DIET ON THE BINDING OF 2-ACETYLAMINOFLUORENE AND ITS *N*-HYDROXY METABOLITE TO RAT LIVER NUCLEIC ACIDS. (E.) Irving, C. C. (VA Hosp., Memphis, Tenn.) T. C. Peeler, R. A. Veazey and R. Wiseman. *Cancer Res* 31(10):1468-1472, 1971.
- 84 ANALYSIS OF MILK SECRETED SPONTANEOUSLY BY VIRGIN RATS BEARING INDUCED MAMMARY TUMORS. (E.) Hallowes, R. C. (Imperial Cancer Research Fund, London, England) and D. J. Lewis. *J Natl Cancer Inst* 51(2):359-368, 1971.
- 85 FURTHER STUDY OF ARTIFICIAL HETEROGENIZATION OF TUMOURS IN THE COURSE OF CHEMICAL CARCINOGENESIS. (E.) Hamburg, V. P. (AMS Inst. of Clin. Oncology, Moscow, USSR), O. Ye. Shcherbina, L. P. Trubcheninova and A. E. Frolzova. *Plasma* 18(5):515-522, 1971.
- 86 ANGIOGRAPHY IN DIMETHYLNITROSAMINE-INDUCED RAT RENAL TUMOURS. (E.) Ekelund, L. (Hosp., Lund, Sweden) and N. Jonsson. *Acta Pathol Microbiol* 11(5):489-96, 1971.
- 87 EFFECTS OF ETHANOL ON MOUSE LIVER POLYSOMAL DISAGGREGATION BY DIMETHYLNITROSAMINE AND CARBOXYCARBOPINE. (E.) Plapp, F. V. (U. Kansas Med. Center, Kansas City), R. D. Updike and M. Chiga. *Exp Cell Res* 18(1):121-123, 1971.
- 88 CHROMOSOME CHANGES AND THEIR EVOLUTION IN SUBJECTS WITH PAST EXPOSURE TO BENZENE. (E.) Forni, A. M. (Devoto Clin., U. Milan, Italy), G. Cappellini, E. Pacifico and E. C. Vigliani. *Environ Health* 23:385-391, 1971.
- 1289 EFFECT OF A CARCINOGENIC HYDROCARBON, 3,4-BENZOPYRENE, ON THE SURVIVAL OF IRRADIATED *E. coli* K-12 BACTERIA. (Rus.) Mirson, I. M. (USSR Acad. Sci., Pushchino), M. M. Vilenchik, Y. N. Runova and B. I. Sukhorukov. *Radiobiologia* 11(5):792-793, 1971.
- 1290 SMOKING HABITS OF PATIENTS WITH GASTRIC CANCER. (E.) Zacho, A. (Finsen Inst., Copenhagen, Denmark), J. Nielsen and V. Larsen. *Acta Chir Scand* 137(5):455-458, 1971.
- 1291 INVESTIGATION ON THE EFFECTS OF CIGARETTE SMOKE ON RABBIT ALVEOLAR MACROPHAGES. (E.) Powell, G. M. (Dept. Med., U. Vermont, Burlington) and G. M. Green. *Biochem J* 124(2):26-27, 1971.
- 1292 CHROMOSOMAL STUDIES IN PATIENTS TAKING PHENYLBUTAZONE. (E.) Stevenson, A. C. (MRC Pop. Genet. Unit, Oxford, England), J. Bedford, A. G. S. Hill and H. F. H. Hill. *Ann Rheum Dis* 30(5):487-500, 1971.
- 1293 HISTOPATHOLOGY OF TUMORS OF CANINE ALIMENTARY TRACT PRODUCED BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE, WITH PARTICULAR REFERENCE TO GASTRIC CARCINOMAS. (E.) Shimosato, Y. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan), N. Tanaka, K. Kogure, S. Fujimura, T. Kawachi and T. Sugimura. *J Natl Cancer Inst* 47(5):1053-1070, 1971.
- 1294 CHANGES IN HEPATIC NUCLEAR DNA-DEPENDENT RNA POLYMERASE CAUSED BY GROWTH HORMONE AND TRIIODOTHYRONINE. (E.) Smuckler, E. A. (Natl. Inst. Med. Res., London, England) and J. R. Tata. *Nature* 234(5323):37-39, 1971.
- 1295 ISOLATION, IDENTIFICATION, AND BIOLOGICAL STUDY OF COMPOUNDS DERIVED FROM 3-METHYLCHOLANTHRENE BY IRRADIATION IN DIMETHYL SULFOXIDE. (E.) Dao, T. L. (New York St. Dept. Hlth., Buffalo, N. Y.), C. King and T. Tominaga. *Cancer Res* 31(10):1492-1495, 1971.
- 1296 INDUCTION OF POLYPLOIDY BY CONCENTRATED THYMIDINE. (E.) Potter, C. G. (Sch. of Med., U. Liverpool, England). *Exp Cell Res* 68(2):442-448, 1971.
- 1297 THYMIDINE LABELING OF PYRIMIDINE ISOSTICHS FROM HUMAN LYMPHOCYTE DNA DURING REPAIR AFTER DAMAGE WITH *N*-ACETOXY ACETYLAMINOFLUORENE OR NITROGEN MUSTARD. (E.) Lieberman, M. W. (Temple U. Sch. Med., Philadelphia, Pa.), J. Z. Rutman and E. Farber. *Biochim Biophys Acta* 247(3):497-501, 1971.

1298 EFFECT OF CYTOSINE ARABINOSIDE AND 1,3-BIS  
(2-CHLOROETHYL)-1-NITROSOUREA ON HEMATOPO-  
IETIC PRECURSORS IN THE MOUSE. (E.) Preisler, H. D.  
(Natl. Cancer Inst., Bethesda, Md.) and E. S.  
Henderson. *J Nat Cancer Inst* 47(5):971-977, 1971.

1299 BIOCHEMICAL CHARACTERIZATION OF PROSTATIC  
NUCLEI: I. ANDROGEN-INDUCED CHANGES IN  
NUCLEAR PROTEINS. (E.) Chung, L. W. K. (Johns  
Hopkins Hosp., Baltimore, Md.) and D. S. Coffey.  
*Biochim Biophys Acta* 247(4):570-583, 1971.

1300 GROWTH INHIBITION OF RAT MAMMARY CARCINOMA  
INDUCED BY CIS-PLATINUM DIAMMINODICHLORIDE-  
II. (E.) Welsch, C. W. (Dept. Anat., Michigan State  
East Lansing,). *J Nat Cancer Inst* 47(5):1071-1078,  
1971.

See also:

- \* (Rev): 1201, 1210, 1214, 1216, 1232
- \* (Immun): 1381
- \* (Path): 1409, 1416



# PHYSICAL CARCINOGENESIS

- 301 "UNSCHEDULED" DNA SYNTHESIS IN HUMAN GERM CELLS FOLLOWING UV IRRADIATION. (E.) Chandley, A. C. (Med. Res. Council, Edinburgh, Scotland) and S. Kofman-Alfaro. *Exp Cell Res* 69(1): 45-48, 1971.

Using autoradiographic techniques, "unscheduled" DNA synthesis was demonstrated in human germ cells following irradiation of UV light. With the exception of spermatozoa, all spermatogenic stages in the testes performed UV-induced "unscheduled" DNA synthesis which was greatest in the late zygotene/early pachytene spermatocytes. Some nuclear DNA synthesis occurred in the unirradiated controls during late zygotene/early pachytene stage of meiotic prophase.

- 302 GAMMA-RAY INDUCTION OF MALIGNANT TUMORS IN RATS. (E.) Hori, C. G. (New England Deaconess Hosp., Boston, Mass.), S. Warren, J. B. Patterson and R. N. Chute. *Amer J Path* 65(2): 79-287, 1971.

The induction of malignant neoplasm in rats using gamma radiation is described. Osteogenic sarcomas were induced in half of the males exposed to gamma radiation adjacent to the bone. This type of tumor, appearing in three males in areas remote from the radioactive sources may not have been due to radiation. Some of the tumors arose from endosteum, others from periosteum. The female rats receiving doses over 20,000 rads failed to develop osteogenic sarcomas. In 14 of 32 rats (44%) parauterine sources of radiation induced adenocarcinoma of the endometrium. Carcinoma of the ovary (12%) was found to be rarer than expected. Carcinomas of the breast were numerous but usually distant from radiation sources. An increased incidence of cancer and a shortening of the latent period were associated with increased total dose and length of exposure time. Cancers frequently failed to develop in spite of extremely high doses (over a million rads to bone and hundreds of thousands to the uterus) suggesting that other factors than dose are involved.

- 303 RADIATION-INDUCED SARCOMA OF BONE. (E.) Arlen, M. (Sloan-Kettering Mem. Inst., New York, N.Y.), N. L. Higinbotham, A. G. Huvos, R. C. Marcove, T. Miller and I. C. Shah. *Cancer* 28(5):1087-1099, 1971.

Twenty-eight cases of radiation-induced osteogenic sarcoma from a series totalling 50 cases studied between 1931-1970 are described. Evidence of preexisting bone pathology in the form of benign osseous growths was seen in 35 cases. Fifteen patients were irradiated for soft-tissue and visceral neoplasms, such as retinoblastoma, seminoma and breast carcinoma, the involved bone lying in the path of the radiation beam. A wide range of pathological findings, from a palpable tender mass in the involved bone to intestinal destruction secondary to metastatic radiation-induced osteogenic sarcoma were seen. It appeared that all bones in the skeletal system were vulnerable. The range of radiation doses covered 1200

rads given in a few weeks to 24000 rads over two years. There was a mean induction time of nine years with a 4-30 year range. Of the patients developing bone neoplasms, 32 have died.

- 1304 RADIATION THERAPY FOR CERVICAL CANCER: LATE EFFECTS ON LIFE SPAN AND ON LEUKEMIA INCIDENCE. (E.) Zippin, C. (Cancer Res. Inst., U. California, San Francisco), J. C. Bailar III, H. Kohn, D. Lum and H. Eisenberg. *Cancer* 28(4): 937-942, 1971.

A review is presented of a continuous study for the investigation of life shortening after partial body exposure to X-rays and/or radium, involving 497 patients with squamous cell cancer of the cervix. The group included only patients that were under 55 at the time of diagnosis who had survived at least five years. Three groups were formed according to dosage: < 23 Mgm-rads, 23-31 Mgm-rads, and 32-54 Mgm-rads. The dose groups were compared with each other within stage and registry, as well as with pooling stages and registries. No statistically significant differences in survival were noted. Although the I.C.R.P. model predicted in excess of seven cases of leukemia for a ten year period, no deaths in this study to date have been attributed to leukemia.

- 1305 ULTRAVIOLET LIGHT, DNA REPAIR AND SKIN CARCINOGENESIS IN MAN. (E.) Epstein, W. L. (Dept. Derm., U. California, San Francisco), K. Fukuyama and J. H. Epstein. *Fed Proc* 30(6): 1766-1771, 1971.

The early nuclear changes of human skin cells *in vivo* occurring after exposure to ultraviolet (UV) light were compared with changes previously detected *in vitro*. Possible mechanisms of UV carcinogenesis are discussed. Autoradiography of epidermal basal cells labeled with <sup>3</sup>H-thymidine after UV exposure and obtained by punch biopsy showed a decrease in incorporation lasting up to 12 hrs. which was longer than the *in vitro* results. Increased incorporation into DNA occurred between two and three days after UV exposure with a return to normal levels by 7 to 14 days. Cells exposed to UV *in vitro* recovered more quickly. Minimal DNA repair *in vivo* was observed up to 12 hrs. after UV exposure in epidermal and upper dermal layers. *In vivo* studies of xeroderma pigmentosum patients confirmed earlier *in vitro* findings that the ability to repair DNA was lacking. DNA replication was normal in 2 of 3 patients. *In vivo* studies on patients with a variety of photosensitivity diseases and/or skin cancers failed to elucidate any DNA repair or replication defects. Attempts to demonstrate inhibition of DNA synthesis by topical application of 0.1% caffeine were unsuccessful. Post-UV intradermal injection of chloroquine, which binds to DNA, inhibited DNA repair and replication in epidermal basal cells.

- 1306 AN AUTORADIOGRAPHIC STUDY ON THE RELATIONSHIP BETWEEN NORMAL AND UNSCHEDULED DNA SYNTHESIS. (E.) Yatani, R. (Mie Prefectural U. Sch. Med., Tsu, Japan), and S. Naruse. *Mie Med J* 20(3): 175-184, 1970.

HeLa cells of a standard line were subcultured for 24 hours prior to exposure to ultraviolet radiation. The cells were then subjected to tritiated thymidine to determine by autoradiographs the rate of pyrimidine substitution in the DNA. It was found that low level irradiation of the nucleus alone, half of the nucleus, or of the whole cell induced repair DNA synthesis. When the rate of repair was measured, it was discovered that DNA synthesis reached maximum shortly after UV exposure and then slowed gradually. These results suggest that unscheduled DNA synthesis is composed of at least two processes: a fast process completed in seven hours more or less after irradiation, and a continuous process which acts for 12 hours or more at a low but constant rate. Finally, it was found that irradiation during the G<sub>1</sub> (pre-DNA synthesis) phase accelerated the initiation of normal DNA synthesis, especially when exposure occurred in the middle or late G<sub>1</sub> period. These findings are discussed in relation to previous works by other authors.

- 1307 DISTRIBUTION OF SKIN CANCERS BY AGE AND SITES. (Ger.) Luger, A. (City Hosp., Vienna-Lainz, Austria). *Wien Klin Wschr* 83(42/43):767-774, 1971

Skin cancers are caused primarily by the cumulative effect of actinic microtraumas which are manifested as a result of radiation intensity and exposure time. Individual susceptibility (pigmentation) also affects carcinogenesis. A survey conducted between 1963 and 1970 by the Dermatologic Clinic of the City Hospital in Vienna analyzed case histories of 1,267 patients with skin cancers and identified four groups of cancers: basal cell carcinomas, 59.6%; metatypical epitheliomas, 13.9%; prickle cell carcinomas, 17%; and keratoacanthomas, 9.6%. Most of the tumors (65-75%) did not become manifest until after the age of 60. The highest incidence of the four types of skin cancers was in the 70.4-year, 72.6-year, 73.8-year, and 70.2-year age group. The decrease in the incidence of skin cancers in older age groups is only a result of the decreasing survival rate. Comparison with the age distribution of the Austrian population disclosed that the incidence of epithelioma increased with increasing age. In contrast, the median incidence age of melanomas, which are not due to a cumulative effect of exogenic noxae, is 57.8 years. The localization of the epitheliomas was found to be closely correlated with the exposure site of the noxae. Regions receiving large amounts of solar radiation are especially affected. Of the 1,267 tumors analyzed, 79.2% were located on head and neck; 81.9% of all tumors were located on regions of the body exposed to light. Another study involving 10,808 epitheliomas located 86.6% of all tumors on the head and 13.4% on the rest of the body. The incidence of skin cancers on lower lids was five times and on the lower lip twice as great

as that on the upper lid and upper lip respectively. A close correlation exists between way of life and exposure to light and localization of skin cancers.

- 1308 POSTIRRADIATION CARCINOMA OF THE LARYNX. (E.) Baker, D. C., Jr. (Columbia-Presbyterian Med. Ctr., New York, N. Y.) and B. Weissman. *Ann Otol* 80(5):634-637, 1971.

- 1309 RADIOSENSITIZATION WITH 5-BROMODEOXYURIDINE OF CHINESE HAMSTER CELLS X-IRRADIATED DURING DIFFERENT PHASES OF THE CELL CYCLE. (E.) Dewey, W. C. (Dept. Radiol. Radiat. Biol., Colorado State U., Ft. Collins), L. E. Stone, H. H. Miller and R. E. Gibrak. *Radiat Res* 47(3):672-688, 1971.

- 1310 SUNLIGHT AND MELANOMA. (E.) Lee, J. A. H. (Sch. Publ. Hlth. Commun. Med., U. Washington, Seattle) and J. M. Merrill. *Lancet* 2(7723):550-551, 1971.

- 1311 LARYNGEAL INTUBATION GRANULOMA. (E.) Elsamra, Y. E. (Ain Shams Fac. Med., Cairo, U. A. R.), I. Mossallam, A. F. El Khodary and A. Y. Habeeb. *J Laryng* 85(9):939-946, 1971.



- 312 SUBCUTANEOUS PAPILLOMATOUS CYSTS PRODUCED BY BOVINE PAPILLOMA VIRUS. (E.) Koller, D. (Dept. Veterin. Sci., U. Wisconsin, Madison) and C. Olson. *J Nat Cancer Inst* 47(4):891-898, 1971.

Subcutaneous papillomatous cysts (SPC) were produced in calves by burial of virus-stimulated skin, autologous skin implants bathed in bovine papilloma suspension (BPS) or burial of experimentally induced cutaneous fibropapillomas. Transplants of papillomas from one donor to a different recipient calf using the use of allogeneic skin implants bathed with BPS failed to produce SPC. A detailed progressive microscopic picture of the developing cyst is given through 21 months of growth. The contents of the cysts were initially a viscous, dry, caseous material that gradually progressed to a fluid containing large clumps of keratinized epithelium. The cysts were found to contain bovine papilloma virus (BPV) and antibody to the virus. A typical cutaneous fibropapilloma developed following surgical exposure of the cysts to the exterior.

- 3 ISOLATION OF HELPER VIRUSES FROM PREPARATIONS OF HAMSTER-SPECIFIC SARCOMA VIRUSES. Kelloff, G. J. (Natl. Cancer Inst., Natl. Inst. H., Bethesda, Md.), R. J. Huebner and R. V. Gilden. *Gen Virol* 13(2):289-294m 1971.

Transforming helper virus (HaLV) was isolated from morphologically normal and cloned transformed hamster cell cultures infected with either Ki-MSV(HaLV) or SV(HaLV) sarcoma virus. Non-producer cell lines carrying sarcoma virus were isolated and virus replication shown to depend on helper virus. Clones shown by a positive complement-fixation test to contain sarcoma virus revealed C-type particles under the electron microscope. Attempts to detect hamster C-type virus activity in hamster embryo fibroblasts infected with defective line sarcoma virus were unsuccessful.

- TUMOUR FORMATION IN HAMSTERS INOCULATED WITH CHICK EMBRYO LETHAL ORPHAN VIRUS. Mancini, L. O. (Dept. Anim. Path., U. Rhode Island, Kingston), V. J. Yates, J. Anderson, V. Miller and L. T. Miller. *J Gen Virol* 13(1):121-126, 1971.

Hamsters from chick tumors induced by chick embryo lethal orphan virus were injected either into cheek pouches or subcutaneously into weanling hamsters, with induction of tumors being more successful in cheek pouches than subcutaneously. Tumors were induced in 95% of the females and in 35% of the males. Oncogenicity was the same in one, two, or three-day-old animals and was shown to be independent of dosage. Twenty-seven of 41 hamsters developed tumors, mostly between the sixth and eighth month after inoculation. All tumors were well circumscribed fibrosarcomas.

- 1315 CHANGES IN CELL MEMBRANE BIOCHEMISTRY UPON TRANSFORMATION IN CULTURE BY TUMORIGENIC DNA VIRUSES. (E.) Mora, P. T. (Natl. Cancer Inst., Bethesda, Md.) and R. O. Brady. *Transplantation Proc* 3(3):1213-1215, 1971.

A search for a well-defined biochemical change which can be consistently found in virus-induced transformation of cells in culture by both SV40 and polyoma virus, and which correlates with the change in growth properties of the transformed cells, revealed the need for a specific transferase involved in the biosynthesis of higher ganglioside homologs. This transferase is repressed in the virally transformed mouse cells but not in those cells lytically infected by polyoma virus. Although it may appear that stable integration of the viral genome is a prerequisite for heritable repression of the transferase, these experiments indicate otherwise. A "flat" or contact-inhibited variant cell that continues to carry viral genes was found; it was capable of repressing the function of the viral genes which altered the growth property and also repressed the repression of the transferase activity. These results have stimulated further experiments now in progress to study correlations between transferase activities, cell membrane biochemistry changes, and tumor specific transplantation antigen activity by means of immune cytotoxicity techniques, as well as by immunogenicity and tumorigenicity in the syngeneic mouse system.

- 1316 THE INFLUENCE OF H-2 TYPE ON GROSS VIRUS LEUKEMOGENESIS IN MICE. (E.) Lilly, F. (Einstein Coll. Med., Bronx, N. Y.) *Transplantation Proc* 3(3):1239-1242, 1971.

Susceptibility and resistance to Gross virus leukemogenesis was found to be associated with the H-2 locus in mice chromosomes. Further analysis showed this locus to have at least two genes associated with it. One of these, called *Rgv-1*, appeared to be closely linked to the H-2 region; the existence of the other gene, however, has yet to be decisively confirmed. The authors attempted to find another gene locus by crossing two inbred mice strains, B10.BR and C3H-OH, both of which were highly susceptible to Gross virus leukemogenesis when inoculated three to five days after birth. When these homozygous non-resistant mice were crossed with each other, it was discovered that the F<sub>1</sub> generation was no longer susceptible to the virus. Thus, the recessive genes for the trait in the parents are not allelic, but rather reside at different loci in the genome. When the F<sub>2</sub> generation was mathematically analyzed for leukemogenesis phenomena, taking "background" from the F<sub>1</sub> generation into account, it was found that the number of genes involved was probably either two or four. A Mendelian genetic model was set up to prove this. Four genotypes were proposed, the phenotypes of which were resistant and susceptible at a ratio of 9:7. Data obtained from the experiment yielded 54% susceptible (105 mice of 194). It appears that genes other than H-2 might determine the success or failure of the virus in infecting host cells, whereupon H-2 type determines whether or not the infection, once established, will lead to the appearance of leukemia.

kemia and to death. It is concluded that H-2 does not appear as an all-or-none determinant of leukemia susceptibility.

- 1317 ASYMPTOMATIC CYTOMEGALOVIRUS INFECTION IN CHILDREN WITH LEUKEMIA. (E.) Armstrong, D. (Mem. Hosp., New York, N.Y.), M. Haghbin, S. L. Balakrishnan and M. L. Murphy. *Amer J Dis Child* 122(5):404-407, 1971.

Forty-two children with acute leukemia were tested for cytomegalovirus (CMV) infection during different stages of the disease. Five patients excreted CMV in either urine or saliva, or both. No virus was detected in peripheral blood samples. Excretion of virus was independent of the stage of leukemia and of antileukemic therapy. There was no detectable correlation between CMV isolation and immunoglobulin levels. Three additional patients had antibody to CMV although no virus excretion could be detected. The course of leukemia did not differ between patients with or without detectable CMV. The incidence of CMV excretion was not found to be higher than that reported from a general pediatric population.

- 1318 MECHANISM OF REOVIRUS DOUBLE-STRANDED RIBONUCLEIC ACID SYNTHESIS IN VIVO AND IN VITRO. (E.) Acs, G. (Inst. Muscle Dis., New York, N.Y.) H. Klett, M. Schonberg, J. Christman, D. H. Levin and S. C. Silverstein. *J Virol* 8(5):684-689, 1971.

The replication of reovirus double stranded RNA (dsRNA) was studied *in vivo* and *in vitro*. Pulse labeling with <sup>3</sup>H-uridine showed that RNA-plus strands were synthesized early in the replicative cycle, followed by synthesis of RNA-minus strands. It was concluded that the plus strands served as synthesis templates for the minus strands. A particulate fraction was subsequently isolated from reovirus-infected cells and was shown to direct *in vitro* synthesis of dsRNA. Polyacrylamide gel electrophoresis of newly synthesized RNA indicated that all ten segments of the viral genome were being produced. Newly synthesized dsRNA was labeled only in the minus strands which further indicated that plus strands served as templates for their synthesis. The particulate fraction was not affected by chymotrypsin or by detergents. Its activity could be destroyed by RNase. The newly formed dsRNA proved to be resistant to ribonuclease digestion at low salt concentrations.

- 1319 THE ROLE OF GENTIC FACTORS IN THE COMBINED NEOPLASTIC EFFECTS OF VACCINIA VIRUS AND METHYLCHOLANTHRENE. (E.) Duran-Reynals, M. L. (Albert Einstein Coll. Med., Bronx, N.Y.), and F. Lilly. *Transplantation Proc* 3(3):1243-1246, 1971.

Studies with inbred mice of different strains revealed a close correlation in the strain distribution of skin

susceptibility to vaccinia virus infection and susceptibility to tumorigenesis by methylcholanthrene (MC) painting. An inverse correlation was found between the skin response to vaccinia virus and MC painting, on the one hand, and the leukemogenic response to MC, on the other. Mice of the BALB/c strain, which are most susceptible to virus-induced skin ulceration and consequent papilloma formation, and which show a low incidence of spontaneous leukemia, were crossed with AKR mice which do not develop skin ulcers or tumors but show a high incidence of spontaneous leukemia. Experimental animals received one mg cortisone acetate s.c. for five days. Vaccinia virus was inoculated intradermally on the day of the last cortisone injection. Animals were painted once daily for five days with 1% MC beginning the day after virus inoculation. The F<sub>1</sub> hybrids showed susceptibility to viral skin infection, but at a much lower level than the parental BALB/c strain. Susceptibility to papilloma production by MC painting was also of lower incidence than in the parental BALB/c strain. The F<sub>1</sub> population, however, showed increased susceptibility to skin ulcer and tumor formation when treated by both vaccinia infection and MC painting (86% incidence). Only 4% of the F<sub>1</sub> hybrids ultimately developed leukemia. In 78% of (BALB/c x AKR) x AKR backcross progeny treated with cortisone, vaccinia and MC showed skin sensitivity similar to the F<sub>1</sub> hybrids, thus suggesting that skin susceptibility to vaccinia is determined by two independent genes. Fifty-six out of 107 of the virus-susceptible mice from the F<sub>1</sub> backcross population developed skin tumors, compared to only two out of 31 virus-resistant mice. About half of the tumors which developed in the virus-susceptible mice progressed to malignancy. These results suggested that MC-induced skin tumorigenesis is determined by one gene which may be independent from those governing skin susceptibility to vaccinia. Results from this F<sub>1</sub> x AKR backcross also showed a correlation between H-2 antigen and the occurrence of skin tumors; this correlation was most evident with the occurrence of malignant tumors. These results compared with those from BALB/c mice indicated that the H-2 locus significantly suppresses skin susceptibility to MC-induced tumors. Study of leukemogenesis with respect to H-2 type, vaccinia susceptibility and skin tumor incidence showed that susceptibility to leukemogenesis and to skin tumor formation are mutually exclusive. A subsequent experiment indicated that the presence of Gross virus infection could inhibit tumorigenesis in MC-treated skin and could delay the onset of leukemia. Since the H-2 locus had previously been associated with susceptibility to leukemia in Gross virus-infected cells, it was considered possible that the apparent interference of natural infection by a leukemogenic virus with skin susceptibility to chemically induced tumors might depend significantly on H-2 type.

- 1320 INDUCTION OF TUMORS IN MARMOSET MONKEYS BY SIMIAN SARCOMA VIRUS, TYPE 1 (*Lagothrix*): A PRELIMINARY REPORT. (E.) Wolfe, L. G. (Rush-Presbyterian-St. Luke's Med. Ctr., Chicago, Ill.), F. Deinhardt, G. H. Theilen, H. Rabin, T. Kawakami and L. K. Bustad. *J Nat Cancer Inst* 47(5):1115-1120, 1971.



marmoset monkeys were inoculated i.m. with an isolate from a naturally occurring fibrosarcoma from a marmoset monkey. The name "simian sarcoma virus, type C" (SSV-1) was proposed for this C-type virus isolate. Seven to 30 days after inoculation the marmosets developed fibromas or well-differentiated fibrosarcomas. Electron microscopic observation revealed type particles in these tumors and in cultures of these tumors. The tumors were characterized according to morphology, clinical course and viral expression. These characteristics were compared to feline sarcoma and Rous sarcoma virus-induced marmoset monkey tumors.

1 IMMUNOFLUORESCENCE STUDIES ON THE TRANSPLANTABLE RAT TUMOR CELLS INFECTED WITH FRIEND VIRUS. (E.) Saito, H. (Hokkaido U. Sch., Japan). *Gann* 61(4):253-258 (and plate LII), 1971.

Analysis of the rejection mechanism of Friend virus-infected tumors by immunofluorescence studies made with three transplantable tumor lines (T-5 sarcoma, DLT lung carcinoma, and AH-109A sarcoma) put into susceptible rats such as Wistar and Donryu. Friend virus partially purified by ultracentrifugations was used for immunization. The indirect method of fluorescent antibody was employed and the rate of both viral and surface antigens was found to be inversely correlated with the growth of Friend virus-infected tumors. A reduction of 35.6 to 70.0% in viral antigens and from 0.06 to 0.34 as fluorescence index in surface antigens was required to produce regression of the tumors. The variation of the fluorescence-positive rate may be due to the difference in grade of antigenicity between tumor lines.

DENSITY CHANGES OF CULTURED BURKITT LYMPHOMA CELLS FOLLOWING EB VIRAL SYNTHESIS. Sugawara, K. (Hokkaido U. Sch. Med., Sapporo, Japan), F. Mizuno and T. Osato. *Nature New Biol* 233(38):107, 1971.

Burkitt lymphoma cells infected with Epstein-Barr virus were successfully separated from uninfected lymphoma cells by centrifugation on discontinuous gum acacia density gradients. Infected cells, identified by immunofluorescence, remained in the upper zone or the top part of the second gradient. The results indicated that infected cells increased in buoyant density as virus synthesis progressed. Cells sedimenting at or near the bottom of the gradient were nonviable. Gum acacia density gradients could possibly be used to separate EB virus-infected cells and also cells carrying different EB virus-associated antigens.

EVIDENCE FOR LINKAGE BETWEEN GENETIC LOCI CONTROLLING RESPONSE OF FOWL TO SUBGROUP A AND SUBGROUP C SARCOMA VIRUSES. (E.) Payne, L. N. (Poulton Poultry Res. Station, England) and P. K. Brown. *J Gen Virol* 13(2):253-259, 1971.

The possible linkage of autosomal loci, "tumor virus a" (*tva*), "tumor virus b" (*tvb*) and "tumor virus c" (*tvc*), which control susceptibility of fowl to infection by subgroups A, B and C, resp., of avian leukosis-sarcoma virus was studied. The responses of fourth generation crosslinked chick embryos from inbred Reaseheath R and W lines indicated the absence of linkage between the *tvb* locus and either the *tva* or *tvc* loci. Strongly associated responses to subgroups A and C suggested either linkage between the *tva* and *tvc* loci or the presence of a single locus which controlled responses to these two subgroups. Analysis of gene frequencies of the three loci were consistent with linkage of *tva* and *tvc*.

1324 GENETIC RESISTANCE TO INFECTION AND ONCOGENESIS BY AVIAN RNA TUMOR VIRUSES. (E.) Crittenden, L. B. (U.S. Dept. Agriculture, ARS Animal Sci. Res. Division, Beltsville, Md.) and W. E. Briles. *Transplantation Proc* 3(3):1259-1264, 1971.

Genetic resistance to virus infection by the avian RNA tumor viruses may be due to a specific receptor molecule required for penetration. No susceptibility to viral subgroups A and B has been demonstrated with alleles of the 11 known blood groups.  $R_1$  (an erythrocyte antigen) has recently been shown to be susceptible to subgroup B viruses. In these studies all embryos possessing  $R_1$  antigen on their erythrocytes were susceptible to subgroup B virus, but some embryos not possessing  $R_1$  were also susceptible. Therefore there may be at least two alleles for susceptibility at this locus. Genetic resistance to oncogenesis of avian RNA tumor viruses has not been completely proven. Resistance demonstrated may be due to a physiologic mechanism or to an efficient immune response to the virus.

1325 HELICAL NUCLEOCAPSID STRUCTURE OF THE ONCOGENIC RIBONUCLEIC ACID VIRUSES (ONCORNAVIRUSES). (E.) Sarkar, N. H. (Inst. Med. Res., Camden, N.J.), R. C. Nowinski and D. H. Moore. *J Virol* 8(4):564-572, 1971.

The internal structures of avian myeloblastosis virus (AvLV), murine leukemia virus (MuLV), murine mammary tumor virus (MTV) and feline leukemia virus (FeLV) as demonstrated by negative staining techniques have several characteristics in common. Some virions penetrated by phosphotungstic acid showed spherical nucleoids with subunit structures composed of strands of nucleoprotein about three nm in diameter arranged in a double helix seven to nine nm in diameter. Most virions, however, had spherical nucleoids with no apparent symmetry. It was postulated that the nucleocapsid of a freshly-budded virus was supercoiled as a hollow sphere. Release of the virus into the extracellular space resulted in uncoiling of the helical nucleocapsid, due to changes in the microenvironment, with subsequent formation of a condensed nucleoid. This resulted in a random arrangement of the nucleoprotein strands. These strands coalesced during formation of

the B particle thus leaving the nucleoid capsule visible. Such coalescence did not occur in formation of the C particle. Thus, the extracellular virion was considered a degenerate form with respect to nucleocapsid structure which explained the fact that helical nucleocapsids were rarely seen in RNA tumor viruses.

1326 DNA IN UNINFECTED AND VIRUS-INFECTED CELLS  
COMPLEMENTARY TO AVIAN TUMOR VIRUS RNA.

(E.) Rosenthal, P. N. (Dept. Med., Stanford U., Stanford, Calif.), H. L. Robinson, W. S. Robinson, T. Hanafusa and H. Hanafusa. *Proc Nat Acad Sci USA* 68(10):2336-2340, 1971.

Studies were conducted using 70S viral RNA hybridized with DNA from infected and uninfected hosts. Hybridization of Rous sarcoma virus (RSV) RNA, Rous associated virus-1 (RAV-1) RNA, RAV-60 RNA and Schmidt-Ruppin-RSV (SR-RSV) RNA with host cell DNA was found to increase  $1.57 \pm 0.15$  times after infection. Hybridization of RSV, RAV-1 or RAV-60 RNA with DNA from chick cells containing RAV-60 in a non-replicating form or from cells which apparently do not contain RAV-60 showed no differences. This indicates that both types of cells contain DNA complementary to several types of virus RNA and that the amount of such hybridizable DNA increases upon viral infection. It thus appears that differences in RNA base sequences of the different avian tumor viruses tested are undetectable by hybridization techniques.

1327 QUANTITATIVE INTERACTIONS OF FELINE LEUKEMIA VIRUS AND ITS PSEUDOTYPE OF MURINE SARCOMA VIRUS IN CAT CELLS: REQUIREMENT FOR DNA SYNTHESIS. (E.) Fischinger, P. J. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.) and D. K. Haapala. *J Gen Virol* 13(2):203-214, 1971.

The characteristics of infection and propagation of feline leukemia virus (FeLV) and the feline leukemia virus pseudotype of murine sarcoma virus (MSV(FeLV)) were studied in cat embryo FEF cells *in vitro*. FeLV rapidly propagated at either high or low infection levels. MSV(FeLV) grew to high titers only if each infected cell was also infected by a replicating unit of FeLV. The first cycle of growth was completed by 40 hrs for FeLV and by about 30 hrs for MLV(FeLV). Although no increase in DNA synthesis could be detected after infection by FeLV or MLV(FeLV), inhibition of DNA synthesis by 20 mM thymidine up to 12 hrs after infection prevented virus replication. DNA synthesis was no longer required after 12 hrs.

1328 *IN VITRO* ISOLATION AND CHARACTERIZATION OF THE GA STRAIN OF FELINE SARCOMA VIRUS (357 83). (E.) Sarma, P. S. (Natl. Cancer Inst., Bethesda, Md.), J. F. Baskar, R. V. Gilden, M. B. Gardner and R. J. Huebner. *Proc Soc Exp Biol Med* 137(4): 1333-1336, 1971.

The Gardner-Arnstein strain of feline sarcoma virus (GA-FSV) was isolated in feline embryo fibroblast cultures from a naturally-occurring feline fibrosarcoma. Secondary and tertiary monolayer cultures of feline embryo fibroblast (FEF) were propagated and prepared as clarified 10% tissue homogenates and as partially purified tumor concentrates. The latter were inoculated in freshly planted cultures of FEF and co-infected with feline leukemia viruses (FeLV). Cell transformation was microscopically examined. Cultures inoculated with tumor concentrate alone contained a nontransforming feline-C-type virus which was identified as GA-FSV-associated virus (GA-FeLV). Both the GA-FSV and the accompanying GA-FeLV were serially propagated in feline and canine embryo cultures. The foci of cell transformation induced by GA-FSV consisted of aggregates of refractile fibroblasts in parallel and crisscross orientations. Evidence was obtained that the development of foci in feline and canine embryo cultures depended on the multiplication of transformed cells rather than in the local spread of virus to adjoining cells. GA-FSV stocks containing high titers of the associated feline leukemia virus gave "one-hit" focus titration patterns in feline and canine embryo cultures. Exogenous "helper" FeLV failed to enhance the focus titers in feline and canine embryo cultures.

1329 LACK OF REQUIREMENT OF MURINE LEUKEMIA VIRUS FOR EARLY STEPS IN INFECTION OF MOUSE EMBRYO CELLS BY MURINE SARCOMA VIRUS. (E.) Levy, J. A. (Natl. Inst. Allergy Infec. Dis., Natl. Inst. Hlth., Bethesda, Md.) and W. P. Rowe. *Virology* 45(3):844-847, 1971.

Evidence points to the need of a helper virus for the replication of sarcoma virus in mouse embryo cells. Several experiments were employed to determine if the sarcoma genome becomes established in the mouse embryo cell when leukemia virus coinfection is absent. Superinfection and infectious center assay methods were used. It was shown that murine sarcoma virus (MSV) can adsorb and enter mouse embryo cells without requiring leukemia virus. Progeny production, however, depends on superinfection with murine leukemia virus (MLV). All foci in the normal rat kidney (NRK) monolayers receiving the Moloney MSV-infected mouse embryo cells as infectious centers were only of the NRK type. The fate of the MSV-infected mouse embryo cell is still unsolved. Studies indicate that possibly, under increased serum concentration, the MSV-infected cell could propagate and register as a focus.

1330 CHARACTERIZATION OF MURINE SARCOMA VIRUS (KIRSTEN) TRANSFORMATION OF MOUSE AND HUMAN CELLS. (E.) Aaronson, S. A. (Natl. Cancer Inst., Bethesda, Md.) and C. A. Weaver. *J Gen Virol* 13(2):245-252, 1971.

The *in vitro* growth characteristics of the Kirsten isolate of murine sarcoma virus (KI-MSV) are reported. KI-MSV was able to produce foci of morphologically altered cells with equal efficiency



rat kidney NRK and NIH/3T3 mouse cell cultures. NIH/3T3 mouse cells were 30 times more resistant to focus formation. Several human fibroblast lines also showed a wide range of susceptibility to focus formation. KI-MSV was found to contain two different viruses, one of which formed foci and the other which formed plaques on XC cells. Results indicated that although the sarcoma virus particle alone is able to transform cells, the presence of helper murine leukemia virus (MLV) was necessary for its replication. The high susceptibility of human cells to KI-MSV was found to be due to the function of the helper virus and not to the sarcoma genome itself. From non-producer KI-MSV-transformed NIH/3T3 cells, four clonal lines of each cell type were obtained. Non-producer clones were morphologically indistinguishable from producer transformed cells. The clonal lines were assayed for MLV antigens. Cellular extracts of each line were negative in complement fixation tests using rat antisera capable of detecting viruses of the murine leukemia-sarcoma complex. However, virus-producing transformants generally showed complement fixation at dilutions exceeding 1:16.

1 ADENOSINE DEAMINASE ACTIVITY IN VIRUS-INDUCED MURINE LEUKEMIA. (E.) Cory, J. (Dept. Chem., U. South Florida, Tampa), A. J. Breno and M. A. Rich. *Enzymologia* 41(4):232-240, 1971.

Some properties of adenosine deaminase in liver extracts from normal and Rich virus infected mice were studied. A five-fold increase in adenosine deaminase activity in the liver of mice infected with Rich leukemia virus was demonstrated. Further studies to compare the properties of the deaminase in liver extracts from normal and Rich virus-infected mice showed a 6.6-fold increase in  $V_{max}$  for the enzyme from the Rich virus infected mice but no differences were observed in the apparent Michaelis constant, the Arrhenius activation energy, the pH optimum, the rate of heat-inactivation or the effect of inhibitors. The marked differences found between extracts from normal and infected mice were in substrate specificity measured by the deaminase activity toward adenosine and 6-chloropurine riboside. Chloropurine riboside was found to be a better substrate for adenosine deaminase from normal liver. Differences were also noted between liver extracts from normal and Rich virus-infected mice in their major bands of deaminase in electrophoretic studies.

2 ADENOVIRUS PROTEINS: III. CELL-FREE SYNTHESIS OF ADENOVIRUS PROTEINS IN CYTOPLASMIC EXTRACTS OF KB CELLS. (E.) Caffier, H. (Saint Louis U. Sch. Med., Mo.), and M. Green. *Virology* 48(1):98-105, 1971.

The synthesis of adenovirus-2 proteins was studied in cell-free cytoplasmic supernatant fractions of infected and 18 hr postinfection KB cells. Labeled amino acid incorporation into hot TCA-precipitable material, which is linear in the complete system for the first 10 to 15 min, levels off after 30 min,

and remains constant up to 100 min, requires the addition of both ATP and GTP. Amino acid incorporation is stimulated by sulfhydryl compounds; RNAase but not DNAase destroys amino acid incorporation; puromycin and cycloheximide inhibit incorporation by 90 to 95% and NaF inhibits by 30 to 40%. Requirements for amino acid incorporation by uninfected and infected fractions differ only in magnesium required, uninfected cells showing a broad optimum and infected cells showing a sharper optimum. Studies concerning release of polypeptide chains indicate that release is maximal after about a 20 min label with about 30 to 40% of protein being recovered in the 100,000 *g* supernatant. Proteins synthesized on ribosomes of a cell-free system were compared with those synthesized *in vivo* and with those of adenovirus-2 virions using polyacrylamide gel electrophoresis. Eight virion polypeptides were identified in the cell-free system, including: capsomere polypeptides, hexon, penton, fiber, hexon-associated protein and internal core protein. No virion protein was found in cell-free extracts of uninfected cells. Proteins synthesized by 18 hr postinfection cell-free fractions were qualitatively the same as those found in late infected cells *in vivo*. No similarities were found between the proteins synthesized in uninfected and in infected cells *in vitro* or *in vivo*.

1333 RELEASE OF ADENOVIRUS MESSENGER RNA FROM ISOLATED NUCLEI. (E.) Raskas, H. J. (St. Louis U. Sch. Med., Mo.). *Nature New Biol* 233(39):134-136, 1971.

Some features of RNA transport were studied *in vitro* utilizing nuclei purified from adenovirus infected cells. These cells release labelled viral RNA as ribonucleoprotein when suspended in a buffer containing ATP and an ATP-generating system. By using *in vitro* studies utilizing isolated nuclei, the problems of heterogeneity of RNA and artifactual binding of cytoplasmic proteins to RNA were avoided. Release of RNA from nuclei was temperature dependent. The sedimentation of the released RNA was studied by layering the post-nuclear supernatant directly onto a sucrose gradient. The released RNA showed two broad peaks. Both components produced during *in vitro* RNA transport contained sequences specific for adenovirus DNA. RNA extracted from the sucrose gradient was annealed to adenovirus type 2 DNA. The size distribution of the RNA released from nuclei *in vitro* suggested that this RNA was not extensively degraded during *in vitro* transport. It was concluded that messenger transport *in vitro* does not require a ribosome subunit to pull the RNA from the nucleus. This conclusion is consistent with the observation that adenovirus RNA newly emerged from nuclei *in vivo* does not cosediment with ribosome subunits. The *in vitro* system described may be an appropriate model for the study of RNA transport in eukaryotic cells.

1334 INTERMEDIATES IN THE SYNTHESIS OF TYPE 2 ADENOVIRUS DEOXYRIBONUCLEIC ACID. (E.) Horwitz, M. S. (Albert Einstein Coll. Med., Bronx, N.Y.). *J Virology* 8(5):675-683, 1971.

Intermediates in the synthesis of adenovirus type 2 DNA were isolated by band sedimentation on alkaline sucrose gradients from infected HeLa S3 cells. The intermediates were all smaller than the viral genome although no fragments as small as the Okayaki fragments were detected when using  $^3\text{H}$ -thymidine labeling from 10 to 240 sec. No addition of nucleotides to the parental genome was seen. The possibility that the intermediates represented breakdown products of DNA was excluded. The synthesis of intermediates during the  $G_2$  phase of the cell cycle, when host DNA synthesis is suspended, the elongation of intermediates to the size of whole viral DNA, and the fact that intermediates are hybridizable to viral DNA, indicated that intermediates represented viral and not host DNA.

- 1335 DIFFERENCE IN SENSITIVITY TO SUPPRESSION OF CELLULAR DNA SYNTHESIS BY ULTRAVIOLET-IRRADIATED ADENOVIRUSES AMONG THREE CELL TYPES. (E.) Yamashita, T. (Nat'l. Inst. Hlth., Tokyo, Japan), Y. Moritsugu, and H. Shimojo. *Japan J Microbiol* 15(5): 473-476, 1971.

Secondary cultures of human embryonic kidney (HEK) cells, green monkey kidney (GMK) cells, and hamster embryo (HE) cells were subjected to infection with prototype strains of adenovirus 2 (Ad 2), 3 (Ad 3), and 12 (Ad 12). Following infection, some of the cultures were irradiated with ultraviolet light for ten minutes. All of the cultures were then pulsed with tritiated thymidine in order to measure DNA synthesis. It was found that DNA synthesis was stimulated by the unirradiated viruses in all three cell lines. On the other hand, DNA synthesis was suppressed by irradiated viruses in the HEK and GMK cells, but was not affected in HE cells. To explain this, viruses were treated with labeled phosphorus and placed on the three cell lines to induce infection. After autoradiographic examination it was discovered that the adsorption of adenoviruses in HE cells was approximately one tenth as efficient as in HEK or GMK cells. The difference in sensitivity to DNA synthesis suppression in HE cells could be due partly to the fact that the virions are not taken up well; however, this theory does not afford a complete explanation. It is suggested therefore that the mode of suppression of cellular DNA synthesis may be different between sensitive and insensitive cells, and if so, the insensitive cells could be used as a control to analyze the regulation of cellular DNA synthesis with the use of UV-irradiated adenoviruses.

- 1336 RESPONSES OF CALF KIDNEY CELLS TO HUMAN ADENOVIRUS TYPE 12. (E.) Kimura, S. (Dept. Bacteriol., U. Tokushima, Japan). *Japan J Microbiol* 15(5):465-471, 1971.

Male calf kidney cells (CKT) were established in culture and were either carried as controls or were subsequently subjected to one of the following four types of human adenoviruses: type 1 (Ad 1, adenoid

71); type 5 (Ad 5, adenoid 75); type 7 (Ad 7, Gomen); or type 12 (Ad 12, Huie). It was found that Ad 1 and Ad 5 grew in CKT cells, but Ad 7 and Ad 12 did not. This was confirmed by complement-fixing antigen tests which showed that Ad 5-infected cells produced antigens but Ad 12-infected cells did not, except for early T antigen. The process of infection was then investigated. Tritiated thymidine was pulsed into normal and infected cultures and, after labeling, the cells from both cultures were sonicated and subjected to various radioactive determination procedures. By scintillation counter, it was found that the CKT cells infected with Ad 12 did not show increased DNA synthesis; rather, Ad 12-infected cells often showed inhibition of DNA synthesis, possibly due to the viral capsid proteins. Further tests also indicated that heat-inactivated Ad 12 had no effect on DNA synthesis, and that addition of UV-irradiated Ad 12 resulted in inhibition of DNA synthesis.

- 1337 MALIGNANT LYMPHOMA WITH LYMPHOCYTIC LEUKEMIA INDUCED IN OWL MONKEYS BY *HERPESVIRUS SAIMIRI*. (E.) Ablashi, D. V. (Nat'l. Cancer Inst., Bethesda, Md.), W. F. Loeb, M. G. Valerio, R. H. Adamson, G. R. Armstrong, D. G. Bennett and U. Heine. *J Nat Cancer Inst* 47(4):837-855, 1971.

Newly recognized features of moderately well-differentiated, malignant lymphoma with lymphogenous leukemia induced in owl monkeys are described. *Herpes saimiri* (HVS), propagated in owl and African green monkey kidney cell cultures and harvested at 80% infectivity, was inoculated intramuscularly into five owl monkeys. Two were then reinoculated with the original inoculum and three were reinoculated with virus from the blood of a once-inoculated monkey. The animals were killed in the terminal phase of the disease, 57-78 days after inoculation. All developed a protracted, moderately well-differentiated malignant lymphoma of the lymphocytic type which was associated with a leukemic phase. Clinical, hematologic, gross necropsy, microscopic and electron microscopic findings are reported in detail. The basic features of this disease were the nearly complete replacement of normal architecture in all lymph nodes by neoplastic lymphocytes, the focally diffuse cellular infiltration into other organ systems, and the presence of many neoplastic lymphocytes in the blood. The cellular infiltration was most consistent and extensive in the lymph nodes, perinodal tissues, spleen, liver, and small intestine, but was present in varying degrees in the mesentery, omentum, pancreas, esophagus, stomach, large intestine, kidneys, adrenal glands, trachea, lungs, heart, epididymis, testes, peripheral nerves, skeletal muscle, periorbital tissues, sclera, lacrimal glands, and brain and meninges. The animals differed primarily in the degree of involvement of specific tissues. The predominant infiltrating cells were moderately well-differentiated lymphocytes. Results suggested that the animals may be viremic for the duration of infection. Results also showed that, during the infection, all animals developed antibody to HVS. HVS was recovered upon cultivation of tissues



- 8 ISOLATION AND CHARACTERIZATION OF A HERPES-VIRUS FROM LEUKEMIC GUINEA PIGS. (E.)  
yak, D. P. (Sch. Med., U. California, Los Angeles).  
*Virology* 8(4):597-588, 1971.

phological and biochemical characteristics of a guinea pig herpesvirus (GPHV) isolated from leukemic strain-2 animals are reported. Mature GPHV virions consisted of an icosahedral capsid with a diameter of 110 nm containing a dense nucleoprotein core surrounded by a double membrane. The mature virion was 166 nm in diameter. Factors affecting GPHV infectivity were the same as those which activated the EB virus of Burkitt's lymphoma. GPHV was related to the guinea pig herpesvirus isolated by Hsiung and Kaplow. Morphological development of GPHV in infected cell monolayers was similar to that of other herpes viruses. Identification of the GPHV genome showed that its DNA was of intermediate in density between the host DNA ( $\rho = 1.700$  g/ml) and herpes simplex DNA ( $\rho = 1.728$  g/ml).

- 9 ONCOGENICITY OF *Herpesvirus saimiri* IN MARMOSSET MONKEYS. (E.) Wolfe, L. G. (Presbyterian-St. Luke's Med. Ctr., Chicago), L. A. Falk and F. Deinhardt. *J Nat Cancer Inst* 47(5):1145-1162, 1971.

Two species of marmoset monkeys and one species of galago were studied to determine their susceptibility to *Herpesvirus saimiri* (HVS). The pathogenesis and behavior of HVS-induced neoplasms and any possibility for transmission of HVS to cage mates by contact, were also studied. All marmosets were susceptible to HVS-induced lymphomas and lymphocytic leukemias (the galago, however, was not susceptible). Determination of the site of i.m. inoculation and of lymph node tissue revealed lymphoreticular proliferation within ten days. HVS infection was invariably fatal, although the course of the disease varied from 35 to 60 days depending upon the marmoset species. Examination of neoplastic tissues failed to elicit the presence of inclusion bodies, viral particles or viral antigens. HVS was present as demonstrated by recovery of the virus from tissues cultured *in vitro*. Ability to recover virus from circulating lymphocytes correlated with the time of appearance of detectable fluorescing and neutralizing antibodies in serum (approximately two to six wk after inoculation). Attempts to transmit HVS by contact were unsuccessful.

- INHERITANCE OF SUSCEPTIBILITY TO ERYTHROCYTE-BORNE BITTNER VIRUS IN MICE. (E.)  
i, S. (Cancer Res. Genet. Lab., U. California, Berkeley), S. Haslam and C. Helmich. *Transplantation* 3(3):1251-1257, 1971.

Series of experiments designed to show the genetically determined susceptibility or resistance to MTV (mouse mammary tumor virus) were conducted. Results confirmed previous reports that R-MTV

causes significant infection in only strains that are histocompatible-2 (H-2) with respect to donors. It was found that mammary tissues are not refractory to allogenic R-MTV. Macrophage-rich peritoneal washing cells from mice immunized against H-2 antigens can significantly reduce R-MTV activity. Based on the results of this and previous studies a model explaining the fate of MTV in susceptible mice was suggested. MTV "B" particles, transported by maternal milk to the young, are carried by the hepatic portal system to the liver. Here the macrophages pick up the virus and transport it to the target cells in the hemopoietic system. R-MTV is produced in the hemopoietic cells and incorporated in the red blood cell fraction of the blood, which carries it until engulfed by macrophages; these then transport the R-MTV to target mammary cells prepared by hormones to render them infectable. The R-MTV then produces both nodule formation and B particles at the mammary tissue level.

- 1341 STRAIN SPECIFICITY IN MOUSE MAMMARY TUMOR VIRUS VIRION ANTIGENS. (E.) Blair, P. B. (Cancer Res. Genetics Lab., U. California, Berkeley). *Cancer Res* 31(10):1473-1477, 1971.

Immunodiffusion studies of mammary tumor virus (MTV) isolated from four strains of mice indicate that at least one antigen of the virion coat is common to all. At least six different antigens could be detected in one or more, but not all, of the four strains tested. It was concluded that the one common antigen was a group-specific antigen of the virion coat. Some of the remaining antigens detected may be considered to be type-specific antigens of the virion coat.

- 1342 PHOSPHOLIPID COMPOSITION OF ROUS SARCOMA VIRUS HOST CELL MEMBRANES AND OTHER ENVELOPED RNA VIRUSES. (E.) Quigley, J. P. (Rockefeller U., New York, N. Y.), D. B. Rifkin, and E. Reich. *Virology* 46(1):106-116, 1971.

It has been postulated that plasma membrane lipids serve as precursors of the lipid in the viral envelope during maturation of the virion in animal cells. To test this hypothesis, Rous sarcoma virus (RSV), Newcastle disease virus (NDV), Sendai virus and Sindbis virus were first grown in cultures of chicken embryo fibroblasts; they were harvested and purified once infection was complete. Initial tests on the viral particles included total dry weight determination, protein and hexose analysis, and RNA extractions; also, the lipid fractions were removed to determine the total dry weight of the lipid and to measure the phospholipid phosphorus and cholesterol levels. The plasma membranes of both infected and noninfected fibroblast cultures were isolated to study the phospholipid content. It was found in preparations over 80% pure that more than 90% of the dry mass of the virus was composed of lipid and protein, the remainder being RNA and

hexose. The purified viruses were made up of 64% protein, 31% lipid (21% phospholipid and 9% cholesterol), 1.9% RNA, and 6% hexose. Total viral phospholipids measurements indicated that 29% of the membrane was composed of sphingomyelin, 28% was phosphatidylcholine, and 30% was phosphatidylethanolamine. It was found that the levels of phospholipids in plasma membranes were basically in agreement for both normal and transformed fibroblasts. However, the viral phospholipids contained a significantly higher proportion of sphingomyelin and a lower proportion of phosphatidylcholine than the plasma membranes. This suggests that the viral lipids may be derived from specialized regions of the plasma membrane which could be specific, and perhaps different, for various enveloped viruses.

- 1343 DEOXYRIBONUCLEIC ACID POLYMERASE OF ROUS SARCOMA VIRUS: REACTION CONDITIONS AND ANALYSIS OF THE REACTION PRODUCT NUCLEIC ACIDS. (E.) Bishop, D. H. L. (Inst. Microbiol., Rutgers U., New Brunswick, N. J.), R. Ruprecht, R. W. Simpson and S. Spiegelman. *J Virol* 8(5):730-741, 1971.

An attempt was made to determine optimal reaction conditions enabling the use of Rous sarcoma virus (RSV) RNA, in undegraded form, to direct the synthesis of product DNA. Product nucleic acid was analyzed using polyacrylamide gel electrophoresis,  $\text{Cs}_2\text{SO}_4$  gradient centrifugation and hydroxyapatite column chromatography. Hydroxyapatite analysis was misleading if viral RNA was present along with DNA. Concomitant monitoring of template RNA is necessary if this method is to be used. Hydroxyapatite analysis of reaction products following resolution by  $\text{Cs}_2\text{SO}_4$  or polyacrylamide gel electrophoresis would be of more value in determining the presence of free single- or double-stranded DNA. Among the factors influencing the polymerase system, detergent concentration was the most critical, with severe degradation of 60S viral RNA occurring at high detergent concentrations. It was concluded that the use of viral 60S RNA containing nicks as template for the reverse transcriptase system might complicate subsequent analysis with artifacts resulting from degraded RNA strands.

- 1344 SPECIFIC INHIBITION OF ROUS SARCOMA VIRUS BY  $\alpha$ -AMANITIN. (E.) Zanetti, M. (Inst. Microbiol., U. Bologna, Italy), L. Foa, F. Costanzo and M. La Placa. *Arch Ges Virusforsch* 34(4):255-260, 1971.

The sensitivity of Rous sarcoma virus (RSV) replication to  $\alpha$ -amanitin, the most powerful toxin of the mushroom *Amanita phalloides*, is described.  $\alpha$ -Amanitin was known to inhibit DNA-dependent extranucleolar RNA polymerase activity. Chicken embryo fibroblast cultures were infected with RSV and treated with  $\alpha$ -amanitin; viral yield of cultures after 24 and 96 hr of cell culture was monitored. Controls were  $\alpha$ -amanitin-treated cultures which were infected with vesicular stomatitis virus (VSV). The viral yield in RSV-infected cultures was severely impaired in the presence of  $\alpha$ -amanitin; in cultures without  $\alpha$ -

amanitin the yield of RSV after 24 hr was 558 focus forming U (FFU)<sup>2</sup>/0.1 ml, while in  $\alpha$ -amanitin-exposed cultures the yield was 7 FFU<sup>2</sup>/0.1 ml. The viral yield in VSV-infected cultures was not affected by  $\alpha$ -amanitin. This indicated that  $\alpha$ -amanitin inhibited RSV replication specifically rather than as a consequence of a nonspecific cellular damage. In long-term experiments, only cell cultures exposed to  $\alpha$ -amanitin from 24-72 hr after infection showed a significant decrease in RSV production. Results indicated that  $\alpha$ -amanitin did not act on the extracellular virus and did not interfere with the very early events (i.e., virus adsorption and penetration) of the infectious cycle.

- 1345 ENZYMES AND NUCLEOTIDES IN VIRIONS OF ROUS SARCOMA VIRUS. (E.) Mizutani, S. (McArdle Lab., U. Wisconsin, Madison) and H. M. Temin. *J Virol* 8(4):409-416, 1971.

The presence of a large number of enzyme activities in purified virions suggested the possibility that some of them might represent cytoplasmic contamination of the virus. A series of experiments showed that, in addition to DNA polymerase, DNA ligase, DNA exonuclease and DNA endonuclease activities, purified virions of Schmidt-Ruppin strain of Rous sarcoma virus (SRV) have nucleotides and nucleotide kinase, phosphatase, hexokinase and lactate dehydrogenase activities. No glucose-6-phosphate dehydrogenase activity could be demonstrated in the SRV virions. Disruption of virions increased the activities of all those enzymes which could be demonstrated in the virions, except for adenosine triphosphatase. The purified virion cores showed DNA polymerase, DNA ligase and hexokinase activities to have a higher specific activity. The role of these components in viral replication is uncertain, but the possibility exists that during assembling of the virions of SRV they may pick up cytoplasmic components which bind to virion proteins.

- 1346 MOLECULAR SIZE OF SIMIAN VIRUS 40-SPECIFIC RNA SYNTHESIZED IN PRODUCTIVELY INFECTED CELLS. (E.) Sokol, F. (Wistar Inst. Anat. Biol., Philadelphia, Pa.) and R. I. Carp. *J Gen Virol* 11(3):177-188, 1971.

A study was made to characterize the molecular size of SV40-specific RNA synthesized in productively infected African green monkey kidney (AGMK) cells. Virus DNA was prepared by propagation of the LP-4 clone of the RH911 strain of SV40 in CV-1 cells, and isolated by treatment of the resulting purified virus particles with phenol followed by chromatography on methylated albumin-kieselguhr columns. Labeled RNA was subsequently isolated from primary monolayer cultures of AGMK infected with SV40. Fractionation of the SV40-specific RNA was effected by velocity centrifugation and subsequent hybridization with excess SV40 DNA. Results showed that: (1) late after infection the virus genome is transcribed into a polycistronic RNA, the size of which is equivalent to or larger than one virus DNA strand; (2) "late" SV40-specific RNA larger than one virus DNA strand



is found in the nuclei, but not in the cytoplasm of infected cells; (3) the predominant species of "late" cytoplasmic SV40-specific RNA, which sediments at 28S, as well as the nuclear 32S to 50S virus-specific RNA, is rapidly degraded into more slowly sedimenting fragments; (4) the "early" SV40-specific RNA synthesized in actinomycin D-treated cells is composed of molecules of appreciably smaller size than one SV40 DNA strand.

- 1347 INHIBITION OF THE SYNTHESIS OF SIMIAN VIRUS 40 ANTIGENS IN CELLS PREINFECTED WITH YABA TUMOR VIRUS. (E.) Tsuchiya, Y. (Lab. Molec. Virol, Southern Illinois U., Carbondale) and H. Rouhandeh. *J Virol* 656-660, 1971.

Infection by SV40 of established lines of cynomolgus monkey kidney cells, previously infected with Yaba virus, failed to induce synthesis of tumor or viral antigens as detected by the fluorescent antibody technique. SV40 was able to replicate in kidney cells not preinfected. The inhibition of SV40 infection by the Yaba virus infected cells was not due to inability of SV40 to adsorb. Although DNA synthesis increased in SV40 infected cells preinfected with Yaba virus, the increase was significantly lower than that observed in SV40 infected cells not preinfected. Attempts to inhibit development of the inhibitory effect against SV40 in Yaba virus-infected cells by cytosine arabinoside were unsuccessful.

- 1348 NUCLEOPROTEIN COMPLEXES IN SIMIAN VIRUS 40-INFECTED CELLS. (E.) White, M. (Dept. Biochem., U. Glasgow, Scotland) and R. Eason. *J Virol* 8(4):363-371, 1971.

Investigation of nucleoprotein complexes in simian virus 40 infected cells indicated that the newly synthesized pools of SV40 DNA in these cells may not occur as free DNA. African green monkey kidney cells (BSC-1) infected with SV40 and then extracted with .25% Triton X-100 after being exposed to tritiated thymidine showed the <sup>3</sup>H-SV40 DNA to be present in a form having a sedimentation coefficient in sucrose gradients of 44S. By means of sensitivity to pronase digestion and labeling with <sup>14</sup>C-amino acids it was shown that the change from the sedimentation coefficient of purified SV40 DNA (21S) was the result of the association of the SV40 DNA in Triton extracts with protein. In short-term labeling experiments with <sup>3</sup>H-thymidine it was found that SV40 DNA molecules in the process of replication were also present as nucleoprotein complexes in Triton-extracted material. Similar amounts of labeled DNA in the form of nucleoprotein complexes were obtained when SV40 DNA was extracted with deoxycholate or Triton.

- 1349 DNA SYNTHESIS IN NORMAL AND VIRUS-TRANSFORMED MAMMALIAN CELLS AFTER METHIONINE DEPRIVATION. (E.) Culp, L. A. (Harvard Med. Sch., Boston, Mass.) and P. H. Black. *Biochim Biophys Acta* 247:220-232, 1971.

The extent of DNA synthesis in cells deprived of exogenous methionine and the degree of methylation in the newly synthesized DNA are described. A comparison of DNA synthesis after methionine deprivation of mouse 3T3 cells and SV40-transformed 3T3 cells was conducted to determine if viral transformation of cells affects the relationship between DNA biosynthesis and its methylation. DNA biosynthesis was seen to continue in methionine-deprived cells as evidenced by the incorporation of bromodeoxy (<sup>14</sup>C)uridine into purified nuclear DNA. The DNA synthesis was appreciable during the first eight hr of deprivation but considerably lower than control values for DNA from cells grown in the presence of methionine. Methionine deprivation resulted in the eventual inhibition of DNA synthesis, either as a result of the inability to methylate DNA or as a result of diminished protein biosynthesis. The newly synthesized DNA in methionine-deprived 3T3 or SV 3T3 cells was deficient (30-40%) in its 5-methylcytosine complement. Methyl-deficient DNA appeared to be stable and was not enzymatically hydrolyzed *in vivo* to acid-soluble nucleotides. It is suggested that mammalian cell DNA biosynthesis is not absolutely dependent upon continued methylation of DNA although synthesis is eventually inhibited without it.

- 1350 THE INHIBITORY ACTIVITY OF DISTAMYCIN A ON X14, H-1 AND POLYOMA VIRUSES MULTIPLICATION. (E.) Castro, A. (Inst. Microbiol., U. Catania, Italy), G. Carrera and G. Russo. *G Batt Virol Immun* 63(11-12):713-718, 1970.

This study seeks to clarify the antiviral mechanism of Distamycin A (DA), an antibiotic produced by *Streptomyces distallicus*. Primary cell cultures of rat embryo and mouse embryo were subjected to DA to determine the reaction of normal cells to the antibiotic. It was found that DA does not interfere with cellular growth and even enhances the multiplication of cells at some concentrations. Mouse and rat cell cultures were then simultaneously subjected to DA and a virus (S.E. polyoma virus Strain 210/22 or picodnaviruses X14 or H-1). Results indicated that virus particles were sensitive to DA, with certain concentrations totally inhibiting viral activity. It was found that the polyoma virus had a higher suppression threshold than did the picodnaviruses. The data indicate that the primary action of DA is on the synthesis of viral DNA, and that the antiviral activity of DA most probably would lie in the inhibition of DNA polymerase. At any rate, some form of selective binding of DA at low concentrations with DNA is likely.

- 1351 GAS CHROMATOGRAPHIC DETERMINATION OF GANGLIOSIDES IN MOUSE CELL LINES AND IN VIRALLY TRANSFORMED DERIVATIVE LINES. (E.) Dijong, I. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.), P. T. Mora and R. O. Brady. *Biochemistry* 10(22):4039-4044, 1971.

- 1352 PURIFICATION OF THE DNA POLYMERASE OF AVIAN MYELOBLASTOSIS VIRUS. (E.) Kacian, D. L. (Coll. Phys. Surg., Columbia U., New York, N. Y.), K. F. Watson, A. Burny and S. Spiegelman. *Biochim Biophys Acta* 246(3):365-383, 1971.
- 1353 PURIFICATION AND PROPERTIES OF CHICK EMBRYO LETHAL ORPHAN VIRUS (AN AVIAN ADENOVIRUS). (E.) Laver, W. G. (Curtin Sch. Med. Res., Australian Natl. U., Canberra), H. B. Younghusband and N. G. Wrigley. *Virology* 45(3):598-614, 1971.
- 1354 SEDIMENTATION EQUILIBRIUM ANALYSIS OF THE MOLECULAR WEIGHT OF A TUMOR VIRUS RNA. (E.) Luborsky, S. W. (Natl. Cancer Inst., Natl. Inst. Hlth., Bethesda, Md.). *Virology* 45(3):782-787, 1971.
- 1355 PATHOGENICITY OF HERPESVIRUS HOMINIS TYPE 2 FOR RABBIT CORNEA. (Jap.) Kobayashi, S. (Yamaguchi U. Sch. Med., Japan), K. Shoji, T. Asayama and M. Kunishi. *Folia Aphthelmologica Jap* 22(8):608-612, 1971.
- 1356 THE EPIDEMIC POTENTIAL OF BRAZILIAN MYXOMA VIRUS (LAUSANNE STRAIN) FOR THREE SPECIES OF NORTH AMERICAN COTTONTAILS. (E.) Regnery, D. C. (Dept. Biol. Sci., Stanford U., California). *Amer J Epidemiol* 94(5):514-519, 1971.
- 1357 CHOLINE METABOLISM AND MEMBRANE FORMATION IN RAT HEPATOMA CELLS GROWN IN SUSPENSION CULTURE: III. CHOLINE TRANSPORT AND UPTAKE BY SIMPLE DIFFUSION AND LACK OF DIRECT EXCHANGE WITH PHOSPHATIDYLCHOLINE. (E.) Plagemann, P. G. W. (U. Minnesota Med. Sch., Minneapolis). *J Lipid Res* 12(6):715-724, 1971.
- 1358 THE NUCLEOTIDE SEQUENCE OF A LOW MOLECULAR WEIGHT RIBONUCLEIC ACID FROM CELLS INFECTED WITH ADENOVIRUS 2. (E.) Ohe, K. (Dept. Med., Yale U., New Haven, Conn.) and S. M. Weissman. *J Biol Chem* 246(22):6991-7009, 1971.
- 1359 PREPARATION OF TYPE 2 HERPES SIMPLEX VIRUS COMPLEMENT-FIXING ANTIGEN. (E.) Palmer, E. L. (Dept. Hlth. Education, Welfare, Atlanta, Ga.), M. L. Martin and D. T. Warfield. *Appl Microbiol* 22(5):925-927, 1971.
- 1360 A TEMPERATURE-SENSITIVE MUTANT OF HERPES SIMPLEX VIRUS DEFECTIVE IN GLYCOPROTEIN SYNTHESIS. (E.) Schaffer, P. A. (Baylor Coll. Med., Houston, Texas), R. J. Courtney, R. M. McCombs and M. Benyesh-Melnick. *Virology* 46(2):356-368, 1971.
- 1361 AN ELECTRON MICROSCOPE STUDY OF RAUSCHER LEUKEMIA VIRUS. (E.) Luftig, R. B. (Duke U. Med. Ctr., Durham, N. C.) and S. S. Kilham. *Virology* 46(2):277-297, 1971.
- 1362 SOME FACTORS AFFECTING INFECTIVITY ASSAYS OF WOUND-TUMOR VIRUS ON CELL MONOLAYERS FROM AN INSECT VECTOR. (E.) Kimura, I. (Dept. Botany, U. Illinois, Urbana) and L. M. Black. *Virology* 46(2):266-276, 1971.
- 1363 THERMOSENSITIVE EVENTS IN THE REPLICATION OF ADENOVIRUS TYPE 2 AT 42°. (E.) Okubo, C. K. (St. Louis U. Sch. Med., St. Louis, Mo.) and H. J. Raskas. *Virology* 46(2):175-182, 1971.
- 1364 VIRAL RNA POLYMERASES: ELECTRON MICROSCOPY OF REOVIRUS REACTION CORES. (E.) Gillies, S. (Dept. Cell. Biol., U. Auckland, New Zealand), S. Bullivant and A. R. Bellamy. *Science* 174(4010):694-696, 1971.
- 1365 HERPES SIMPLEX VIRUS: GENOME SIZE AND REDUNDANCY STUDIED BY RENATURATION KINETICS. (E.) Frenkel, N. (Dept. Microbiol., U. Chicago, Ill.) and B. Roizman. *J Virol* 8(4):591-593, 1971.
- 1366 ULTRASTRUCTURAL CHANGES IN FRIEND ERYTHROLEUKEMIA CELLS TREATED WITH DIMETHYL SULFOXIDE. (E.) Sato, T. (Sloan-Kettering Inst. New York, N. Y.) C. Friend and E. D. Harven. *Cancer Res* 31(10):1402-1417, 1971.
- 1367 A COMPARATIVE STUDY OF SOME OF THE ENZYMES INVOLVED IN GLUCOSE METABOLISM OF HUMAN DIPLOID AND SV40-TRANSFORMED HUMAN DIPLOID CELLS. (E.) Dunaway, G. A., Jr. (Dept. Chem., U. Oklahoma, Norman) and E. C. Smith. *Cancer Res* 31(10):1418-1421, 1971.
- 1368 AMYLOIDOSIS, IMMUNOCOMPETENCE, AND THE CHRONIC MURINE DISEASES INDUCED BY REOVIRUS TYPES 1 AND 2. (E.) Phillips, P. A. (Dept. Microbiol., U. Western Australia, Perth), M. N-I. Walters, N. F. Stanley and D. Keast. *Pathology* 3(4):267-76, 1971.
- 1369 ELECTRON MICROSCOPY OF FRIEND MURINE LEUKEMIA VIRUS IN THE MID-GUT OF EXPERIMENTALLY INFECTED MOSQUITOES. (E.) Hirumi, H. (Boyce Thompson Inst., Yonkers, N. Y.), G. J. Burton and K. Maramorosch. *J Virology* 8(5):801-804, 1971.

See also:

- \* (Rev): 1205, 1206, 1207, 1210, 1212, 1219, 1220, 1223
- \* (Chem): 1285
- \* (Immun): 1375, 1379, 1385
- \* (Path): 1412
- \* (Epid-Biom): 1425



- 370 DEPRESSION OF DELAYED HYPERSENSITIVITY BY PRETREATMENT WITH FREUND-TYPE ADJUVANTS: DESCRIPTION OF THE PHENOMENON. (E.) Asherson, G. (Clin. Res. Ctr., Northwick Park, Harrow, England) and G. G. Allwood. *Clin Exp Immun* 9:249-258, 1971.

Pretreatment with FCA (Freund's complete adjuvant) given alone, can prevent the delayed hypersensitivity reaction induced by antigen in FCA when given with bovine  $\gamma$ -globulin (BGG), human serum albumin or arsanil-N-cetyl tyrosine. The 24 hr skin reactions were depressed ranging from 25 to 75%. Four hour skin reactions were also depressed. Hemolytic and cytotoxic antibody to BGG was not affected by pretreatment with FCA when BGG in FCA was used for immunization. Pretreatment with FCA or *Corynebacterium parvum* adjuvant depressed hypersensitivity to BGG induced by BGG in either *C. parvum* adjuvant or FCA, showing that pretreatment and immunization do not necessarily have to be the same. Pretreatment with FCA and soluble antigen acted synergically in depressing the 24 hr delayed skin reactions in both the guinea pig and the rat. This depression of hypersensitivity was greater in these animals than pretreatment and immunization observed with either FCA or soluble antigen alone. The effect of the depression of antibody production caused by soluble antigen was not altered by pretreatment with FCA. Experiments in the mouse showed depressed contact sensitivity to picryl chloride induced by picryl chloride in FCA following pretreatment with *C. parvum* adjuvant or FCA. Pretreatment with FCA did not depress contact sensitivity to picryl chloride and oxazolone induced by skin painting.

- 371 DEPRESSION OF DELAYED HYPERSENSITIVITY BY PRETREATMENT WITH FREUND-TYPE ADJUVANTS: MECHANISM OF THE PHENOMENON. (E.) Allwood, G. (London Hosp. Med. Coll., England) and G. L. Asherson. *Clin Exp Immun* 9:259-266, 1971.

Depression of certain inflammatory responses by Freund's complete adjuvant (FCA) was demonstrated. The four hr Arthus reactions following passive transfer of antiserum to bovine  $\gamma$ -globulin (BGG) and human serum albumin were depressed in recipient guinea-pigs by pretreatment with FCA alone. Depressed 24 hr delayed reactions following passive transfer of guinea peritoneal exudate cells and serum were demonstrated in recipient outbred guinea-pigs and white rats. Transfer to normal recipients of the 24 hr reactions which were produced in guinea-pigs and white rats pretreated with FCA alone, then immunized with BGG in FCA, suggest that the central state of delayed hypersensitivity which normally follows immunization with BGG in FCA is depressed by pretreatment with FCA. The reduced delayed hypersensitivity skin reactions depressing the inflammatory response and the central state of immunity demonstrated by these experiments may apply to certain human diseases of unknown etiology such as Sjögren's disease, sarcoidosis and primary biliary cirrhosis which depress delayed hypersensitivity skin reactions in a similar manner.

- 1372 ANTIBODY FORMATION FOR MALIGNANT TUMOR: II. ANTIGENICITY OF EHRlich ASCITES TUMOR. (E.) Yamamoto, Y. (Okayama U. Med. Sch., Japan), Y. Tadatomo and S. Okamura. *Acta Med Okayama* 24(5):527-536, 1971.

The *in vitro* antitumor activity of immune-serum produced by low density lipoprotein obtained from a mouse tumor transplanted with JTC-11 cells is reported. Using the dextran sulfate precipitation method the low density lipoprotein in tumor of dd mice transplanted with JTC-11 cells was prepared. This low density lipoprotein showed a single band in electrophoresis with a different mobility than that of other organs. The typical chemical composition of cholesterol, lipid and phospholipids was found in the tumor low density lipoprotein. The inhibition of tumor growth by immune serum was most marked at the 25th day after the intraperitoneal administration of tumor low density lipoprotein. The  $\gamma$ -globulin contained the main fraction effective for inhibition of tumor growth.

- 1373 ANTIBODY FORMATION FOR MALIGNANT TUMOR: III. ANTIGENICITY OF PEPTIDE OF RIBOSOMAL DIGEST IN EHRlich ASCITES TUMOR. (E.) Yamamoto, Y. (Okayama U. Med. Sch., Japan), D. Jituki and Y. Yabuki. *Acta Med Okayama* 24(5):537-547, 1971.

The specific peptide of the ribosome of Ehrlich ascites tumor was examined, and an antitumor activity of serum from mice immunized with this peptide was demonstrated. DEAE Sephadex A50 column chromatography was used to purify the peptides. Peptides showed the following characteristics: 1) 1.32S<sub>20w</sub> sedimentation constant; 2) basic and single electrophoretic properties; 3) maximum absorbancy at 267 m $\mu$ . The immunization with the purified peptide was carried out in mice and rabbits. Using JTC-11 cells the inhibitory effect of the immune  $\gamma$ -globulin on the tumor growth was demonstrated. The Ouchterlony double diffusion chamber and immunoelectrophoresis studies showed a single precipitin line between rabbit antiserum and tumor cell extracts of Ehrlich ascites cells. A precipitin line was found at the  $\beta_2$ - $\gamma$  region in immunoelectrophoresis.

- 1374 IMMUNOLOGIC STUDIES OF HUMAN BREAST CANCER: I. SERUM REACTIVITY AGAINST A LYMPHOID CELL LINE (BELEV) DERIVED FROM A BREAST CANCER PATIENT AS DETECTED BY COMPLEMENT-FIXATION TEST. (E.) Chan, S. P. (Bionetics Lab., Bethesda, Md.), R. D. Maca, P. L. Levine and R. C. Ting. *J Nat Cancer Inst* 47(3):511-517, 1971.

Results of complement-fixation (CF) tests for detection of the reactivity of sera from breast cancer patients against an antigen preparation from a tissue-cultured pleural effusion (Belev) from a breast cancer patient are described. Sera from patients with solid cancers, including cancer of the mouth, colon, skin and cervix, were also tested against the Belev cell line. Of 92 breast cancer sera, 45%

had antibody titers ranging from 1:8 to 1:128 to Belev cell antigen. The incidence of antibody to the Belev cell line was 16% in 97 patients with other solid cancers, 13% in patients with breast diseases other than cancer, and 5% in normal subjects. To determine the reactivity of sera from breast cancer patients and others against preparations of cells containing HLA isoantigens, sera were tested against antigen prepared from 3 lymphoid cell lines: Raji cells (from a patient with Burkitt's lymphoma), IM-1 cells (from an infectious mononucleosis patient) and 4265 cells (from a leukemia patient). Twenty percent of sera from patients with breast cancer reacted with the lymphoid cell line antigen. In patients with other solid cancers, the incidence of reactivity was similar. Only 5% of patients with breast diseases other than cancer showed reactivity against this antigen, and none of the normal sera showed detectable reactions. Three percent of sera from breast cancer patients and 4% of sera from patients with other solid tumors reacted against a phytohemagglutinin-stimulated normal lymphoid antigen from normal lymphoid cells. Of 41 Belev antigen-positive sera from breast cancer patients, 17 were also positive against the lymphoid antigen. The antibodies detected may have been reacting against tumor-associated antigens of the Belev cells.

- 1375 IMMUNOSUPPRESSION BY LEUKEMIA VIRUSES: VII. STIMULATORY EFFECTS OF FRIEND LEUKEMIA VIRUS ON PRE-EXISTING ANTIBODY-FORMING CELLS TO SHEEP ERYTHROCYTES AND *Escherichia coli* IN NON-IMMUNIZED MICE. (E.) Hirano, S. (Albert Einstein Med. Ctr., Philadelphia, Pa.), H. Friedman and W. S. Ceglowski. *J Immunol* 107(5):1400-1409, 1971.

The mechanism of Friend leukemia virus-induced enhancement of "background" antibody-forming cells was studied in non-immunized BALB/c and C57BL/6 mice. The number of "background" cells against sheep erythrocytes (S-RBC), as determined by plaque assay, increased rapidly after infection. The rate of increase and magnitude of the response was proportional to the injected virus dose. The increase in "background" cells with activity against *E. coli* was not marked. Leukemia-resistant C57BL/6 mice injected with FLV showed an insignificant increase in "background" antibody-forming cells to either S-RBC or *E. coli*. Heat and formaldehyde-inactivated FLV also failed to elicit a significant response. Enhancing activity of FLV could not be accounted for by the presence of nucleic acids or cell debris in the virus preparations. Presence of a cross-reacting antigen between the virus preparation and *E. coli* or S-RBC was also eliminated. It was concluded that the mode of action of FLV probably involved FLV causing proliferation of pre-committed antibody-forming cells or precursors to these cells.

- 1376 IMMUNOGLOBULINS ON THE SURFACE OF LYMPHOCYTES: IV. DISTRIBUTION IN HYPOGAMMAGLOBULINEMIA, CELLULAR IMMUNE DEFICIENCY, AND CHRONIC LYMPHATIC LEUKEMIA. (E.) Grey, H. M. (Nat'l. Jewish Hosp. Res. Ctr., Denver, Colo.), E. Rabellino and B. Pirofsky. *J Clin Invest* 50(11):2368-2375, 1971.

The distribution of surface antigen-containing peripheral lymphocytes was studied by immunofluorescence in normal humans and in those with chronic lymphatic leukemia (CLL), cellular immune deficiencies, selective IgA deficiency and sex-linked or acquired agammaglobulinemia. Twenty-eight percent of normal peripheral lymphocytes contained surface IgA, 15% contained IgG, 6%, IgA and 8%, IgM. The kappa:lambda ratio was 2:1. Lymphocytes from CLL patients contained only a single immunoglobulin. Seventy-five percent of the cases studied had an IgM H chain class and the remaining 25% had no detectable H chain. Twelve cases had a kappa L chain class and 8 had a lambda L chain. All four patients with sex-linked agammaglobulinemia and the one case of acquired agammaglobulinemia showed very few (e.g., 1% to 2%) lymphocytes with surface immunoglobulin. All three patients with IgA deficiency had normal immunoglobulin-positive lymphocytes, including IgA, although no serum IgA could be detected. Patients with immune deficiencies all had either a normal or decreased level of immunoglobulin-positive lymphocytes.

- 1377 IMMUNOHISTOLOGIC STUDIES OF CARCINOMA OF THE PROSTATE: I. HUMAN IgG ANTIBODIES TO STRUCTURAL COMPONENTS OF RABBIT LIVER. (E.) Ablin, R. J. (Millard Fillmore Hosp., Buffalo, N.Y.) and W. A. Soanes. *Ann Clin Res* 3(4):226-230, 1971.

The fluorescent antibody method was used to demonstrate the presence of circulating antibodies in the sera of patients with benign and malignant diseases of the prostate. Sera from 24 patients in various clinical stages of carcinoma were combined with a fluorescein-conjugated goat anti-human IgG preparation. This mixture was placed on unfixed cryostat sections of rabbit liver; the reaction revealed the presence of antibodies to liver nuclei and/or to bile canaliculi in carcinoma-infected patients. Specifically, 17 of the 24 patients showed the presence of antibodies reacting with bile canaliculi, which is thought to be of pathologic significance. Only six patients, however, showed antibodies to liver nuclei, probably representing nonspecific indicators of the presence of other immunologic processes. The frequency of IF staining reactions of human IgG antibodies to nuclei and/or bile canaliculi of rabbit liver in all cases studied, the range in titer, and incidence in relation to the stage in carcinoma were considered, although no attempt was made to correlate the intensity of staining with the stages. It is concluded that while antibodies have been demonstrated, the significance of such antibodies is not clear, and further studies are needed to elucidate their nature and function.

- 1378 TOPOGRAPHY OF CELL SURFACE ANTIGENS. (E.) Stackpole, C. W. (Sloan-Kettering Inst. Cancer Res., New York, N. Y.) *Transplantation Proc* 3(3):1199-1201, 1971.

The topography of cell surface antigens using electron microscopic methods, in which models are cons-



constructed from serial sections showing the distribution of labeled antigen over the entire cell surface, is reported. The indirect hybrid antibody method is used with either southern bean mosaic virus (SBMV) or ferritin as visual markers. High and low resolution models for the study of murine leukemia viruses are discussed. The freeze-etching technique, advantageous in that it gives a more accurate view of the cell surface and attached markers, as well as giving a large amount of information rapidly from a large number of cells is referred to briefly.

- 379 IMMUNOSUPPRESSION AND ONCOGENIC VIRUS INFECTION. (E.) Hirsch, M. S. (Harvard Med. Sch., Boston, Mass.), P. H. Black and M. R. Proffitt. *Cell Proc* 30(6):1852-1857, 1971.

Experimental models are discussed in relation to the possible role of oncogenic viruses in the development of cancer in immunosuppressed states. Evidence cited indicated that oncogenic viruses which were either acquired from the environment or activated within host cells may have been a necessary intermediate. It is postulated that immunosuppression may have prevented rejection or elimination of the virus, the transformed cell, or both. The most feasible method of preventing malignancies in immunosuppressed states may be to induce nonimmunologic defense mechanisms such as interferon production or phagocytosis by reticuloendothelial cells.

- 380 ISOLATION OF 7S IgM AND KAPPA CHAINS FROM THE SURFACE MEMBRANE OF TISSUE CULTURE CELLS DERIVED FROM A BURKITT LYMPHOMA. (E.) Eskeland, T. (Karolinska Inst., Stockholm, Sweden) and E. Klein. *J Immunol* 107(5):1368-1375, 1971.

The liberation and characterization of 7S IgM and kappa chains from the surface of Daudi tissue culture cells, a permanent line derived from Burkitt lymphoma, is described. Freezing and thawing, or homogenizing Daudi cells caused the release of mu and kappa structures. Density gradient centrifugation and Sephadex G-200 gel filtration of the supernatant fraction from previous ultracentrifugation showed the presence of 7S IgM molecules and free kappa chains. The sediment, which consisted of membrane and cell particles, had an excess of membrane-associated kappa structures compared to membrane-associated mu structures determined by inhibition of passive hemagglutination.

- 381 EVIDENCE OF THE NONIMMUNE REGRESSION OF CHEMICALLY INDUCED PAPILLOMAS IN MOUSE SKIN. (E.) Andrews, E. J. (Sch. Vet. Med., U. Pennsylvania, Philadelphia). *J Nat Cancer Inst* 47(3):653-665, 1971.

Experiments are reported which were designed to determine whether immunity is an effective mediator of

papilloma regression; the immune response in mice was experimentally suppressed and the pattern of regression of 3-methylcholanthrene (MCA)-induced papillomatous allografts was observed. Allografts were taken from C3H and BALB/c female mice which had been topically exposed to MCA-impregnated filter material. Allografts were grafted onto C3H or BALB/c mice; recipients had been immunosuppressed by a combined regimen which included thymectomy, exposure to 450 R of radiation and antithymocyte serum injection. In two series of experiments, the combined incidence of papillomas arising on skin-grafted immunosuppressed mice was 63.5%; 80.4% of papillomas in both series regressed, despite the fact that allografts remained healthy and in place. Neither cellular nor humoral immunity could be detected in graft recipients. Regression was slow and gradual. Papillomas showed a propensity to regress at  $21 \pm 4$ -day intervals. This clustering pattern in papilloma regression was not seen in immunocompetent mice. Regressions in immunosuppressed mice were apparently the result of a nonimmunologic mechanism.

- 1382 ANTINUCLEAR ANTIBODIES IN THE SERA OF NASOPHARYNGEAL CARCINOMA PATIENTS. (E.)

Yoshida, T. O. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan), M. Takada, A. Kawamura, Jr., C.-S. Yang, S.-M. Tu, C.-H. Liu and Y. Ito. *Gann* 10:283-289, 1971.

An investigation using indirect immunofluorescence to demonstrate anti-nuclear antibody in the nucleus of human nasopharyngeal carcinoma cells (NPC) is reported. Anti-nuclear antibody was detected by immunofluorescence using ten cell lines from NPC biopsy materials and sera collected from the same NPC patients. None of the cells of these lines possessed detectable amounts of SV40 T-antigen, adenovirus 12 T-antigen, or Epstein-Barr virus antigen. Cultured human embryo lung cells, NPC cells, and Raji cells (from a patient with Burkitt's lymphoma), were also used as target cells for the detection of anti-nuclear antibodies in sera of NPC patients. Definite anti-nuclear antibody was detected in 26 of 97 Chinese NPC cases and in one of 15 Japanese cases. Thirty-nine normal healthy sera did not show any specific reaction within the nucleus of cultured cells. It was thought that anti-nuclear antibodies in sera of NPC patients were heterophilic. There was no evidence that the NPC patients involved in this study had anti-nuclear antibody-producing autoimmune diseases. Four nuclear staining patterns were seen in cultured NPC cells: a "diffuse" pattern; a "speckled" pattern; a "nucleolar" pattern; and a "nucleolar combined with speckled" pattern.

- 1383 ANTIBODIES TO HERPES-TYPE VIRUS, HERPES VIRUS, ADENOVIRUS, AND REOVIRUS IN NASOPHARYNGEAL CARCINOMA PATIENTS IN TAIWAN. (E.) Yang, C.-S. (Coll. Med., Natl. Taiwan U., Taipei), S.-H. Hsieh, M.-M. Hsu, Y.-C. Lin and A. Kawamura, Jr. *Gann* 10:199-207, 1971.

To determine whether viruses other than those of the

herpes-type are involved in nasopharyngeal carcinoma, 200 serum specimens from histopathologically confirmed nasopharyngeal carcinoma patients and additional specimens from a healthy control group were studied. The histopathologic sera were divided into high and low groups based on antibody titers, while the control sera were considered as a whole. The incidence of infection with adenovirus (type 7, strain: Gomen, and type 12, strain: Huie), herpes simplex, and/or reovirus (type 1, strain: Lang, and type 2, strain: D5) in all groups was compared. Analyses included indirect immunofluorescent antibody reactions, neutralization reactions, complement fixation studies, and hemagglutination inhibition detection. It was found that the rate of reo-1 virus infection in the herpes-type virus low titer group was significantly higher than in the high titer group, but the same as in the control group. No statistical difference was seen although more reo-2 virus infection was found in the herpes-type virus high titer group than in the low titer group. Adeno- and herpes-type virus infection rates showed little difference between the two carcinoma groups, but the positive rates of herpes complement-fixing and Ad7 neutralizing antibodies in the control group were higher than those of carcinoma patients, who had more Ad7-T antibodies than Ad12-T. However, there was no correlation between anti-Ad-T and anti-herpes-type virus titers. Based on this data, a close relation of tested viruses other than herpes-type viruses to nasopharyngeal carcinoma could not be established, because highly significant differences in infection rates of candidate viruses were not found among high- and low-titer groups and control groups.

- 1384 ANTIGEN ANALYSIS ON SERUM FROM CATTLE WITH LEUCOTIC TUMOURS. (E.) Brummerstedt, E. (Roy. Veterin. Agricult. U., Copenhagen, Denmark) and H. J. Bendixen. *Acta Path Microbiol Scand B* (79):699-707, 1971.

Serum samples, originating from cattle with leukosis, were examined for possible antigenic changes by an absorption technique in immunodiffusion and immunoelectrophoresis. It was shown that there was a decreased capability of absorbing antibody against serum from non-leukotic animals, due either to an absence or decreased level of a certain protein component, possibly IgM. However, loss or change in concentration of IgM did not seem to be specific for leukosis, since it was missing in four animals with other diseases. The existence of specific serum proteins for leukosis could not be demonstrated.

- 1385 HETEROTRANSPLANTATION OF TWO HUMAN LYMPHOID CELL LINES TRANSFORMED *IN VITRO* BY EPSTEIN-BARR VIRUS. (E.) Deal, D. R. (Div. Biol. Stndrd., Bethesda, Md.), P. Gerber and F. V. Chisari. *J Nat Cancer Inst* 47(4):771-780, 1971.

Data on the heterotransplantability, in neonatal mice treated with antilymphocyte serum, of two human cell

lines transformed *in vitro* by Epstein-Barr virus (EBV) are presented. Human lymphoblastoid cell lines AV<sub>1</sub> and JQ established from EBV-seronegative normal human adult donors by exposing leukocytes to EBV, were injected i.p. into (BALB/c x A/HeN)F<sub>1</sub> mice in the first 24 hr of life; mice had been pretreated with antilymphocyte serum. Of 30 mice given  $1 \times 10^7$ - $10^8$  AV<sub>1</sub> cells, 28 developed tumors and died; of 40 mice given lower doses, none died. The critical dose of AV<sub>1</sub> cells was  $1 \times 10^7$  cells. Postmortem, mice presented a grayish-white hemorrhagic gelatinous tumor mass enveloping stomach, small and large intestines, liver and spleen. Tumors metastasized to retroperitoneal structures and to the abdominal and diaphragmatic musculature. Tumor cells were basically undifferentiated lymphoid cells, but some tended toward histiocytic and lymphoblastic differentiation. The invasive and aggressive nature of tumor cells was revealed by their penetrating mucosa of hollow organs. There was conspicuous sparing of the heart by metastatic tumor. All ten mice inoculated with  $1 \times 10^7$  JQ cells developed tumors and died. Of 11 mice given  $5 \times 10^6$  JQ cells, seven died tumors, but survival was longer than with the larger dose. Doses of less than  $5 \times 10^6$  JQ cells failed to cause fatal tumors. The gross pathology of the JQ animals was similar to that of the AV<sub>1</sub> animals, except that the tumor mass in the JQ group was less bulky and more vascular in appearance than in the AV<sub>1</sub> group. Buffy-coat lymphocytes from donors without serologic evidence of EBV infection failed to proliferate when inoculated in mice; one of the EBV-seronegative donors of buffy-coat lymphocytes contributed the cells from which the AV<sub>1</sub> line was established.

- 1386 SURFACE ANTIGEN EXPRESSION IN MALIGNANT SUBLINES DERIVED FROM HYBRID CELLS OF LOW MALIGNANCY. (E.) Grundner, G. (Karolinska Inst., Stockholm, Sweden), E. M. Fenyö, G. Klein, E. Klein, U. Bregula and H. Harris. *Exp Cell Res* 68(2):315-322, 1971.

Experiments were conducted in which Ehrlich ascites tumor cells were fused with three L cell derivatives, A9, B82 and A9R1, then tested for the surface antigens. Membrane immunofluorescence and mixed hemadsorption tests were used to examine for H-2<sup>k</sup> isoantigen, virus-induced Moloney-type antigen and L antigen which were the three surface antigens contributed to the hybrid cells by the L cell derivatives. Complete or partial suppression of these surface antigens was demonstrated in hybrid cells. Although the hybrid cell lines showed a low level of malignancy, an occasional segregant subline of high malignancy was thrown off. The three surface antigens reappeared independently of each other in the malignant sublines and a substantial chromosome loss was noted. The results of this study suggested that the Ehrlich cell possessed mechanisms for the suppression of surface antigens which were lost in the segregant tumors.

- 1387 REMARKABLE ENHANCEMENT OF TRANSPLANTABLE TUMOR GROWTH BY ANTISERUM PREPARED FROM THE HEAVIER LYMPHOCYTE FRACTION. (E.) Kinoshita, Y. (Osaka City U., Med. Sch., Japan) and S. Kimura. *Exp Cell Res* 68(2):471-476, 1971.



the enhancing effect of anti-HSL antiserum on the growth of transplanted Walker's carcinosarcoma and the difference in the immunosuppressive activity of antisera from HSL and LSL fractions are reported. Transplanted tumor growth was markedly enhanced by rabbit antiserum (AHLAS, corresponding to rat heavier lymphocyte fraction when compared with normal serum). ALLAS (corresponding to the lighter lymphocytes) had an augmenting effect, but its activity was not as apparent as that of AHLAS. The enhancing effect disappeared when AHLAS was absorbed by the heavier lymphocytes. This absorptive ability of the ALLAS was weak. The results indicate a possible qualitative difference between HSL and LSL as well as the possibility that AHLAS may have been a more effective immuno-suppressor of lymphocytes than ALS.

1388 PROGRESSIVE DEVELOPMENT OF CHEMICAL CARCINOGEN-INDUCED SKIN TUMOR AND OF TRANSPLANTED CARCINOMA WITH AN IMMUNOSUPPRESSOR. (E.) Moto, N. (Fac. Pharmaceut. Sci., U. Tokyo, Japan), Kato, D. Mizuno and S. Takayama. *Gann* 62(4): 1-300, 1971.

The stimulative effect of the immunosuppressor, azathiopurine, on the development of 3-methylcholanthrene (3-MCA)-induced skin tumors and on that of mid type Ehrlich carcinomas was examined. Male and female mice aged six to seven weeks were either given pretreatment with azathiopurine or were not pretreated. The animals were then given single s.c. injections of Ehrlich carcinoma cells followed by daily azathiopurine post-treatments. It was found that mice without the pretreatment showed a slightly inhibited growth of carcinoma, while pretreated mice exhibited enhanced growth rates reciprocally dependent on the dose of post-treatment azathiopurine. Mice were then either treated or not treated with azathiopurine prior to 3-MCA application to the dorsal epidermis. After application, azathiopurine injections were either resumed or not resumed. Mice receiving pre- and post-treatments with azathiopurine had the highest incidence of malignant and benign tumors of all groups. Mice receiving only 3-MCA painting had only benign tumors, as did animals receiving only pre-treatment plus the carcinoma. Finally, RES activity (indicating the immunosuppressive state) was measured using labeled gold. It was found that the administration of higher doses of azathiopurine during 3-MCA stimulation inhibited RES activity, but lower doses plus 3-MCA or 3-MCA alone did not show any inhibitory effect. These observations show that the effect of azathiopurine is twofold: one effect is produced by pretreatment and the other is found when a lower dose of azathiopurine is given subsequently during the whole period of the experiment. In addition, the progress of carcinogenesis after azathiopurine treatment is parallel with the depression of RES activity, showing that azathiopurine depresses the immunologic reaction of the host.

1389 RNA-MEDIATED TRANSFER OF TUMOR IMMUNITY-- A NEW MODEL FOR THE IMMUNOTHERAPY OF CANCER. (E.) Deckers, P. J. (Nat'l. Cancer Inst., Nat'l. Inst. Hlth., Bethesda, Md.) and Y. H. Pilch. *Cancer* 28(5): 1219-1228, 1971.

Normal spleen cells were incubated with RNA isolated from rats immunized against benzo(a)pyrene-induced fibrosarcoma (BP-IR) to transfer tumor-specific transplantation immunity. Both male and female Fischer 344/N rats were used. The development of tumor isografts was decreased in rats which received intravenous injections of spleen cells treated in the above manner. When "immune RNA" from spleen and from nodes of BP-IR guinea pigs was mixed with dextran sulfate, which inhibits ribonuclease, a reduction in the incidence of tumor development was also noted. Dextran sulfate alone was ineffective. The possible use of "immune" RNA in human cancer patients was discussed.

1390 ON THE IMMUNOLOGICAL FACTORS IN THE DEVELOPMENT OF THE TROPHOBLASTIC TUMORS. (Jap.) Shiraki, S. (Gifu U. Sch. Med., Japan). *Acta Sch Med Univ Gifu* 18(6):947-960, 1971.

The immunological host-tumor-relationship in hamsters in which normal human trophoblasts and hydatidiform moles were transplanted was investigated. When the viability of the grafts was confirmed, the immunizing effect of anti-lymphocyte serum (ALS) on the persistence or proliferation of the trophoblast in the host was then studied. It was found that the survival time of the normal human trophoblast was prolonged by treatment with ALS. In the group of hamsters not receiving ALS, rejection occurred within about one week. Histological examination of this group showed a type of rejection phenomenon. Hydatidiform moles transplanted in hamsters not receiving ALS survived about 20 days as compared to 50 day survival in hamsters given ALS treatment. Rejection phenomena were observed in tissues of both ALS-treated and -untreated animals; in neither group, however, were rejection reactions pronounced. It was concluded that the development of trophoblastic tumors suggested the existence of the immunological tolerance on the part of the host. It was assumed that attenuation of the antigenicity of the malignant trophoblast may be related to development of the trophoblastic tumor.

1391 PHA SHORT-TERM CULTURE OF LYMPHOCYTES IN ACUTE LEUKEMIA DURING REMISSION: RELATION WITH THERAPY. (E.) Lo Curto, M. (Pediat. Clin. U. Palermo, Italy) and B. Liuzzo. *Acta Haemat* 45(6): 337-343, 1971.

The PHA-induced blastogenesis in lymphocyte cultures of 28 acute leukemia patients in remission and four normal subjects were studied by autoradiography. The following results were obtained: 1) lymphocytes of patients untreated for more than two weeks demonstrated normal blast transformation; 2) lymphocytes

of patients in treatment with 6-mercaptopurine or methotrexate showed normal blast transformation in some cases, but in others lacked blastogenesis. These results suggest that the lymphocytes are sensitive to the immunodepressive action of the mentioned antimetabolites, while in other patients the lymphocytes are resistant to that action. This is of interest since clinically the therapeutic action of the antimetabolites was always found to be efficient.

- 1392 IMMUNOFLUORESCENT LOCALISATION OF HUMAN ALPHA FETOPROTEIN IN FETAL AND NEONATAL LIVERS AND CULTURED CELLS FROM HEPATOCELLULAR CARCINOMA. (E.) Smith, J. A. (Dept. Path., U. Ibadan, Nigeria), T. I. Francis, G. M. Eddington and A. O. Williams. *Brit J Cancer* 25(2):343-349, 1971.

A study dealing with the localization of the site of production of alpha fetoprotein (AFP) by immunofluorescent technique is presented. Liver portions from an aborted fetus, an autopsied neonate, and necropsied patients who had shown AFP in their sera were examined. From cryostat sections in the fetal and neonatal liver, most of the fluorescence was periportal in localization. The fluorescence in each positive cell was homogeneous and limited to the cytoplasm. In the liver of AFP seropositive hepatocellular carcinoma, fluorescence was present either in single cells or in a clump of cells (not more than five). In tissue cultures, at least one positive cell was seen in each of the four AFP positive liver cell carcinoma cultures. A few clumps of fluorescent cells were seen in a more recent culture from a positive hepatoma. Morphologically, all the cells were fibroblast-like; cultures from malignant tumors showed greater variations in cell size with more mitotic figures. It is possible that reported AFP-positive and -negative cells become malignant concurrently or that the intrinsic AFP-positive cells give rise to both AFP-positive and -negative hepatocytes. The indirect immunofluorescent technique is considered as sensitive as the double diffusion method for the detection of AFP.

- 1393 CELL-FREE PASSIVE TRANSFER OF DELAYED HYPERSENSITIVITY TO CHEMICALS IN GUINEA PIGS. (E.) Burger, D. R. (Dept. Microbiol., U. Arizona, Tucson) and W. S. Jeter. *Infection Immunity* 4(5):575-580, 1971.

Leukocytes obtained from peritoneal exudates, lymph nodes and alveolar washings of guinea pigs sensitized to 2,4-dinitrochlorobenzene (DNCB) and 2,4-dinitrofluorobenzene (DNFB) were incubated in Hank's balanced saline. This cell-free incubation medium, when injected intraabdominally into untreated animals, was able to confer delayed hypersensitivity to DNCB and DNFB. The cell-free transfer material was purified on Sephadex G200 columns and found to

be a dialyzable substance of small molecular size. It is temperature stable for 30 min at 56°C and for 9 wk at -65°C. The active fraction has a 280 nm to 260 nm absorbance ratio of 0.71. The release of transfer activity by leukocytes was found to depend on pH with greatest release at slightly acidic levels.

- 1394 CORRELATION OF IMMUNOLOGICAL RESPONSIVENESS WITH LYMPHOCYTE IN CHICKENS INFECTED WITH MAREK'S DISEASE. (E.) Evans, D. L. (Dept. Anim. Sci., U. Arkansas, Fayetteville) and L. T. Patterson. *Infection Immunity* 4(5):567-574, 1971.

An attempt was made to correlate the immunological, hematological and pathological responses in chickens with Marek's disease. About one-half of Marek-infected chickens previously injected with *Salmonella pullorum* antigen failed to respond to a challenge. The antibody titers of chickens which did respond were decreased during the first and second weeks after inoculation. Twenty-four percent of the group responding to antigenic challenge had leukemia compared to 54% of those unresponsive. White blood cell counts were increased in Marek's disease-infected chickens. Large lymphocytes and blast cells were increased in number to a greater extent in chickens unresponsive to challenge. As many as 30% of disease-infected chickens had low hematocrits throughout the testing period. Chickens unresponsive to antigenic challenge showed a higher mortality rate and incidence of gross lesions than did responsive chickens. Infected chickens not receiving antigen had a lower mortality rate and gross lesion incidence than did infected chickens which received antigen.

- 1395 CHEMOTHERAPY, IMMUNOCOMPETENCE, IMMUNOSUPPRESSION AND PROGNOSIS IN ACUTE LEUKEMIA. (E.) Hersh, E. M. (U. Texas, Anderson Hosp. Tumor Inst., Houston), J. P. Whitecar, Jr., K. B. McCredie, G. P. Bodey and E. J. Freireich. *New Eng J Med* 285(22):1211-1216, 1971.

The relation of immunocompetence to the response to therapy was investigated in 25 adults with acute myelogenous leukemia. It was generally found that a suppressed immune response is associated with a poor response to chemotherapy whereas immunocompetence is correlated with complete or partial remission. Eighty-six percent of patients showing normal delayed hypersensitivity underwent remission compared to 25-50% of unresponsive patients. The lymphocytes of patients not achieving remission showed a subnormal response to *in vitro* stimulation by phytohemagglutinin-M. The most effective immunosuppression in patients receiving chemotherapy was found to occur when administration of antigen preceded treatment by five to eight days. Immunological response was greatest in those given antigen one day prior to treatment. It was concluded that monitoring immunological response in patients with acute leukemia may identify patients with good prognoses.



GROWTH OF MOUSE MAMMARY TUMOR RELATED TO HOST RESISTANCE. (E.) Takeuchi, S. (Jpn. J. Cancer Res. Clin. Oncol., U. Tokyo, Japan) and H. Uchida. *Cancer* 62(2):77-87, 1971.

Spontaneous mammary tumors and the established R1887 line, MM2, from a spontaneous mammary tumor were characterized quantitatively according to their growth characteristics with special reference to host resistance. Autografts and isografts on C3H/He mice pretreated by whole body X-irradiation showed a cube root growth pattern. Normal mice survived  $44.8 \pm 0.68$  days whereas resistant mice survived for  $58.0 \pm 1.65$  days. MM2 implants showed no growth and subsequent regression in mice with a high resistance. Growth was linear, after a latency period, in both normal and low-resistance mice. Results also indicated that growth rate of MM2 implants in normal mice varied from cube root growth pattern (inoculum of  $2 \times 10^4$  or more cells) to simple exponential growth with inocula of  $4 \times 10^{-3}$  or fewer cells. Injection i.p. of MM2 cells into highly resistant hosts resulted in significant detection of tumor cells. Growth of MM2 tumor cells was repressed in hosts already bearing spontaneous mammary or MM2 tumors. It was therefore concluded that tumor-bearing hosts still have the capacity of an immune response against their tumor.

HUMAN LYMPHOCYTE PROLIFERATION: DNA SYNTHESIS TIME. (E.) Schiffer, L. M. (Allegheny Gen. Hosp., Pittsburgh, Pa.). *Cell Tissue Kinetics* 4(6):585-595, 1971.

A dual labeling technique is used to determine the synthesis time ( $T_s$ ) *in vivo* and *in vitro* for solid tumor tissue taken from patients with Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma. Patients received  $^3\text{H}$ -thymidine i.v. Surgical specimens were minced in the presence of  $^{14}\text{C}$ -thymidine, embedded, and autoradiographs were prepared. Lymphocytes were classified according to size and cytoplasmic basophilia into four groups: A (small, nonbasophilic), B (small, basophilic), C (large, nonbasophilic) and D (large, basophilic). The  $T_s$  of splenic lymphocytes of patients with Hodgkin's disease were: B, 11.3 hr, C, 10.4 hr, and D, 8.4 hr. Type A lymphocytes did not label sufficiently to determine their  $T_s$ . Lymphocytes taken from tissues containing Reed-Sternberg cells generally showed an increased  $T_s$ . The  $T_s$  for lymphosarcoma was 10.4 to 14.6 hr, and that for reticulum cell sarcoma was 7.5 to 7.7 hr. The problems and assets of the dual labeling technique for determining  $T_s$  were discussed.

ANTITUMOR EFFECT OF LYMPHOCYTE AND MACROPHAGE FROM MICE IMMUNIZED WITH EHRlich TUMOR CELLS. (E.) Sakashita, T. (Mie Prefectural U. Sch. Med., Tsu, Japan). *Mie Med J* 20(3):241, 1970.

*In vivo* and *in vitro* studies were carried out to clarify which of two immune cell types were of primary importance in the immune response. Ehrlich ascites tumor cells were treated with nitrovin and then were injected i.p. into inbred DS male mice. Immunity was later determined by challenging the mice with untreated tumor cells. All immune animals were then subjected to one of three experiments. In the first, *in vivo* cellular responses of the immunized mice to the i.p. challenge of tumor cells were examined through the peritoneal exudates. It was found that after challenge the numbers of lymphocytes and mononuclear cells increased reactively by 12 hours, reached maximum between 24 and 48 hours, and after 72 hours decreased as the tumor cells disappeared. The number of macrophages began to increase from 12 to 24 hours and were still increasing after 72 hours despite the disappearance of the tumor cells. In the second part of the experiment, *in vitro* reactions were analyzed between the tumor cells and the immune cells, the nonimmune cells, or the serum from immune or nonimmune cells. It was discovered that both immune and nonimmune sera had no effect on the tumor cells. In addition, cultured macrophages did not cause any significant morphologic change. However, tumor cells were destroyed when cultured with the viable immune lymphocytes. In the third study, the passive transfer of immunity was studied by subjecting inbred DS or C57BL male mice to initial injections of lymph node cells derived from immune DS mice, and to secondary injections of tumor cells. It was found that only viable immune lymphocytes could accomplish the passive transfer of immunity in the syngeneic system. In the homologous system, however, almost all the recipients could reject the tumor cells, even if the transferred cells were nonimmune ones.

1399 IMMUNOGLOBULINS DURING THE COURSE OF ACUTE LEUKEMIA IN CHILDREN: EFFECTS OF VARIOUS CLINICAL FACTORS. (E.) Gooch, W. M., III (Dept. Pediat., Texas Children's Hosp., Houston) and D. J. Fernbach. *Cancer* 28(4):984-989, 1971.

The IgA, IgG, and IgM immunoglobulin levels, studied serially in 19 children with acute leukemia, show no apparent relationship with the hematologic status of the patient, with or without blood transfusion therapy. Chemotherapy or infection appeared to be related to any major changes found. Prednisone plus vincristine may have had a greater immunosuppressive effect than prednisone plus 6-mercaptopurine but, to date, there is insufficient evidence for confirmation. The largest variation was seen in the IgG levels, but the amount of depression of each of the three classes indicated the possibility of a common chemotherapeutic mechanism. Failure of the child to respond to infection was not associated with low IgG levels. Children with acute leukemia, regardless of status of the disease retained the ability to produce immunoglobulins in response to infection.

1400 EXPRESSION OF SURFACE ANTIGENS ON CULTURED TUMOR CELLS IN RELATION TO CELL CYCLE.

(E.) Cikes, M. (Karolinska Inst. Sch. Med., Stockholm, Sweden). *Transplantation Proc* 3(3):1161-1166, 1971.

About two weeks after infection with Moloney leukemia virus (MLV), JLS-V9 cells derived from Balb/c bone marrow showed the presence of cell surface antigens specified by the H-2 locus and MLV and detected by immunofluorescence tests. Further cultivation revealed a cyclic pattern of appearance and disappearance of the surface antigens similar to patterns observed in other systems. Antigen expression varied inversely with cell volume. JLS-V9 cells were synchronized using 0.04 µg/ml colcemid for four hours and the expression of surface antigen in relation to the cell cycle was studied. Maximal expression was found during the G<sub>1</sub> period. As cells entered the S phase, antigen expression dropped and remained low throughout S and G<sub>2</sub>. Similar results were obtained using synchronized Daudi cells, a human lymphoblastoid line derived from a Burkitt tumor. Disappearance of cell surface antigens was observed by prelabeling cells with fluorescein-tagged antibody and scoring for disappearance of fluorescence over a 24-hour period. Disappearance of label was fastest in cells maintained at 37°C (<10% labeled after 24 hrs). Cells maintained at 24°C showed only a 30% decrease in labeling whereas cells maintained at 0°C lost only 10% of their label. Disappearance of antigen thus depends on cell metabolism. The rate of disappearance of label is also inversely proportional to cell concentration. The possibility of dissociation at the alloantigen-alloantibody or at the alloantibody-antialloantibody connections is not excluded; however, it is considered unlikely. Several possible mechanisms which might be responsible for cyclic expression of surface antigen are discussed.

1401 CELL-MEDIATED IMMUNE REACTION TO TWO GYNECOLOGIC MALIGNANT TUMORS. (E.) DiSaia,

P. J. (U. Texas M. D. Anderson Hosp. Houston), F. N. Rutledge, J. P. Smith and J. G. Sinkovics. *Cancer* 28(5):1129-1137, 1971.

A study of cell-mediated immune reaction to two malignant tumors, an advanced squamous cell carcinoma of the cervix and an adenocarcinoma of the ovary, is reported. Peripheral blood lymphocytes from patients with these tumors were cytotoxic to the tumor cells *in vitro*. The tumor-specific surface antigens from the malignant tumors seem to behave like transplantation antigens. It appears that physical contact is necessary for cytotoxic effect of the lymphoid cells. Growth was not inhibited by lymphocytes from regional lymph nodes in these patients. Patients with these malignancies appear to circulate presensitized peripheral blood lymphocytes which have the potential for immediate interaction *in vitro*, in contrast to lymphocytes from normal healthy individuals which show a delayed cytotoxic effect.

1402 AN INCREASE OF SERUM ALPHA-GLOBULIN IN TUMOR-BEARING HOSTS AND ITS IMMUNOLOGICAL SIGNIFICANCE. (E.) Ashikawa, K. (Inst. Med. Sci., U. Tokyo, Japan), K. Inoue, T. Shimizu and Y. Ishibashi. *Jap J Exp Med* 41(4):339-355, 1971.

The humoral factor, alpha-globulin, is thought to play an important role in immune tolerance. Two separate studies were conducted to test the significance of such a hypothesis. The first study used serum specimens from 81 cancer patients, 41 non-cancer patients, and 10 healthy individuals. Serum albumin values averaged 60% in the cancer patients, 67% in the non-cancer patients, and 70% in healthy individuals. Alpha<sub>1</sub>-globulin and alpha<sub>2</sub>-globulin studies showed cancer patients with a mean value of 3.4% and 12.0%, respectively, non-cancer patients with 2.8% and 9.2%, and healthy individuals with 2.0% and 8.2%. The relative increase of serum alpha-globulin in cancer patients paralleled an increase of mucoprotein in alpha<sub>1</sub>-globulin fractions. In the second study, C3H/He/Jms, BALB/c/Jms, and DDD mice were inoculated s.c. with ascitic type mammary carcinoma MM2 cells or ascitic type hepatoma MH134 cells. Once the mice were tumor-bearing, they were subjected to immunobiological analyses. It was discovered that: 1) an increase of serum alpha-globulin and mucoprotein occurred, as in the human cancer sera tests; 2) the thymus was atrophied with progressive tumor development; 3) migration of leucocytes was depressed, with leucocyte counts variable throughout the tumor-bearing stage; and 4) survival time of tumor-bearing animals was shortened by administration of alpha-globulin. In addition, prolongation of the survival of skin homografts occurred in normal mice given alpha-globulin immediately after grafting surgery. Also, lymphoid cells from both normal and tumor-bearing mice demonstrated significant immunologic suppression when transferred with alpha-globulin to newborn mice. It was concluded that alpha-globulin in tumor-bearing hosts nonspecifically blocks an antigenic site on the surface of lymphocytes and weakens antigenic recognition of the lymphoid cells; it is different from enhancing antibody which coats the target cells and avoids immunologic attacks.

1403 ULTRASTRUCTURAL LOCALIZATION OF HL-A ANTIGEN AT CELL SURFACE. (E.) Kourilsky, F. M.

(Hosp. St.-Louis, Paris, France), D. Silvestre, C. Neaupoit-Sautes, J. Dausset and J. P. Levy. *Transplantation Proc* 3(3):1203-1207, 1971.

1404 CARCINOMA OF THE TESTIS IN A RENAL TREATMENT RECIPIENT. (E.) Leb, D. E. (U. Pittsburgh, Sch. Med., Pa.) and R. S. Howell. *Amer J Med Sci* 262(3):171-174, 1971.

1405 DIFFERENCES IN LEUKOCYTE REACTIVITY AGAINST ANTINUCLEAR ANTIBODIES IN PATIENTS WITH BL MALIGNANCIES: A NEW PROOF OF THE ABNORMAL CHARACTER OF THE NONLEUKEMIC CELLS OF THESE PATIENTS. (Fr.) Duc J. (I.N.S.E.R.M., Toulouse, France), E. Ohayon and F. Oksman-Domejean. *Bull Acad Nat Med* 155(21-22):490-494, 1971.



1406 ROLE OF ACTIVATED MACROPHAGES AND ANTIBODY  
IN INHIBITION AND ENHANCEMENT OF TUMOUR  
GROWTH IN RATS. (E.) Keller, R. (Immunol. Res.  
Group., U. Zurich, Switzerland) and V. E. Jones.  
*Lancet* 7729:847-849, 1971.

1407 IMMUNOGLOBULINS ON THE SURFACE OF HUMAN  
LYMPHOCYTES. (E.) Papamichail, M. (Canadian  
ed Cross Mem. Hosp., Maidenhead, England), J. C.  
Brown and E. J. Holborow. *Lancet* 7729:850-852, 1971.

1408 LYMPHOCYTE REACTIVITY IN CANCER. (E.) Field,  
E. J. (Newcastle Gen. Hosp., Newcastle upon  
Tyne, England) and E. A. Caspary. *Lancet* 7729:877-  
878, 1971.

See also:

- \* (Rev): 1202, 1203, 1204, 1205, 1206, 1218,  
1229, 1230, 1231
- \* (Chem): 1258, 1284, 1285
- \* (Viral): 1341, 1347, 1368

- 1409 STUDIES ON THE HISTOGENESIS OF EXPERIMENTALLY INDUCED BRAIN TUMORS: II. CYTOLOGICAL OBSERVATIONS IN CELL CULTURES. (Ger.) Thust, R. (Med. Acad., Erfurt, Germany), R. Warzok and G. Osske. *Exp Path* 5:217-225, 1971.

*In vitro* studies of a methylnitrosourea (MNU)-induced brain tumor in a Hauben rat cultivated *in vivo* for over 40 generations are presented. Specimens studied were from the 14th, 20th and 26th transplants. Two distinct varieties of cells were observed in all cell cultures. Ameboid  $\alpha$ -cells growing in dense monolayers in a sickle-shaped pattern and exhibiting phagocytic activity decayed selectively within three weeks, to be gradually replaced by fibroblastoid  $\beta$ -cells. The malignancy of this latter category was verified by homotransplants to six rats which died of brain tumor within 18-21 days following inoculation. Histochemical differences between the two cell categories included different sites for nonspecific esterase, acid phosphatase and NADH-tetrazolium reductase which were spread throughout the cytoplasm in the  $\beta$ -cells. Application of 2'-deoxy-5-fluorouridine (2  $\mu$ g/ml medium for 72 hr) to two day old primary cultures of the 20th transplant generation and subsequent inoculation (following trypsin treatment) to newborn rats produced tumors referred to as AZ tumors. The tumors revealed a high  $\alpha$ -cell proliferation tendency *in vitro* and typical epithelioid features upon long-term culture, with a total lack of  $\beta$ -cells. Cytophotometric measurements of DNA and chromosomes showed these cells to be of the triploid and tetraploid types. The frequency distribution of chromosomal counts, carried out in 71 mitoses, indicated a maximum of 74 chromosomes per cell. The occurrence of scattered mitoses with hexa- or heptaploid chromosome sets indicated that the rarely encountered peak DNA values were not to be interpreted as due to S- or G<sub>2</sub>-phase-determined DNA increase, but rather resulted from increasing chromosomal numbers. The total lack of polymorphous cells within these tumor cultures was attributed to their multiple transplantations performed before the first *in vitro* observations.

- 1410 MANIFOLD CHROMOSOME OBSERVATIONS IN ACUTE MYELOGENOUS LEUKEMIA. (E.) Obara, Y. (Chromosome Res. Unit, Hokkaido U. Japan), M. Sasaki and S. Makino. *Gann* 62(4):301-308, 1971.

Chromosome studies from peripheral blood and marrow samples of ten patients with acute myelogenous leukemia were examined directly and following three-day cultures of the samples, with and without phytohemagglutinin. Five cases showed a normal karyotype. The remaining five showed: two cases with a presumptive C/G translocation, one hyperdiploid case with 52 chromosomes, one case showing a Ph<sup>1</sup> like chromosome, and one case with a ring chromosome. Abnormal karyotypes undetectable by the direct method were found by blood and marrow cultures without phytohemagglutinin.

- 1411 MYOGENOUS ORIGIN OF A GRANULAR CELL TUMOR OF THE URINARY BLADDER. (E.) Christ, M. L. (Michael Reese Hosp. Med. Ctr., Chicago, Ill.), and L. Ozzello. *Amer J Clin Path* 56:736-749, 1971.

In an ultrastructural study of a human granular cell tumor of the urinary bladder, myofilaments were demonstrated, confirming the myogenous derivation of this neoplasm. These findings were in contrast to electron microscopical findings in other granular cell tumors which are interpreted as having a Schwannian histogenesis. The findings in this study indicated that granular cell tumors may have different cell type derivations.

- 1412 LEAKAGE AS THE SOURCE OF OVERGROWTH STIMULATING ACTIVITY IN ROUS SARCOMA TRANSFORMED CULTURES. (E.) Bissel, M. J. (Dept. Molec. Biol., U. California, Berkeley), H. Rubin and C. Hatié. *Exp Cell Res* 68(2):404-410, 1971.

Primary cultures of C/O or C/B type chick embryos and RIF-free embryos were established as viable cell lines and then infected with the Bryan high titer strain of Rous sarcoma virus (B-RSV), the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV), or the nontransforming Rous associated virus (RAV). At various intervals after infection, the cells and media were assayed for overgrowth stimulating factor (OSF), thought to be dislocated intra-cellular material which leaves the transformed cells due to altered membrane properties. The chemical marker used was the intracellular soluble enzyme, lactic dehydrogenase (LDH). It was found that as the total level of overgrowth stimulating activity rose in the RSV-transformed cultures the level of LDH rose, both within the cells and in the media. The increase was higher and faster in B-RSV- than in SR-RSV-infected cells. This was correlated with the degree of transformation: B-RSV transforms the culture more rapidly and completely than the SR-RSV. The cells infected with RAV did not show a corresponding increase over normal levels, indicating that transformation and not virus infection was responsible for the OSF increase. Also, the appearance of both OSF and LDH in the media of transformed cultures indicated that these cells "leaked" more than normal cells. Of importance, therefore, are the degree of transformation, age of the cells, and various changes in pH which would affect leakiness or cell death. The parallel increase in intra- and extracellular OSF levels raises the question of the relation of these two parameters to each other and to transformation. The nature of the active component of OSF and the significance of the rise of LDH levels is yet to be determined.

- 1413 PAGET'S DISEASE OF THE VULVA. (E.) Fenn, M. E. (U. Michigan Med. Ctr., Ann Arbor), G. W. Morley and M. R. Abell. *Obstet Gynec* 38(5):660-670, 1971.

The clinical and pathologic findings of seven Caucasian patients (averaging 67 years of age) with Paget's disease of the vulva are reported. Involvement included the labium majus in all seven patients, perineal skin in three, and the labium minus in three. Paget cells were shown in several sweat ducts in two patients, b



uch cells were found in the epidermis and in the scattered pilosebaceous structures in all seven patients. Surgical treatment varied from hemivulvectomy in some to radical vulvectomy in others. Proven recurrence was shown in only one case. Underlying invasive carcinoma was not seen in any of the seven patients, however other proven primary malignant neoplasms were found in three of the patients. No predisposing factors to Paget's disease have been uncovered to date, but a multifocal autochthonous origin in the epidermis and its appendages is likely. As yet, the exact prototypic cell remains in doubt. Vulvar biopsies for diagnosis are stressed.

1414 PROFILE AND POSSIBLE ORIGIN OF AN ADRENOCORTICAL CARCINOMA. (E.) Dluhy, R. G. (Peter Bent Brigham Hosp., Boston, Mass.), J. J. Marlow, E. M. Mahoney, R. L. Shirley and G. H. Williams. *J Clin Endocr* 33(2):312-317, 1971.

A ten year clinical profile of a 30 year old female with amenorrhea and hirsutism is presented. The patient showed an elevation in her 16-ketosteroid for 9 years prior to emergence of an adrenocortical carcinoma. During the ten year period, laboratory tests revealed suppression of the ketosteroids following glucocorticoid therapy. The patient died 4 mo. after removal of the primary neoplasm of metastatic carcinoma. At autopsy, the microscopic findings showed the nontumorous adrenal gland (20 g) to be hyperplastic, suggesting a possible abnormal function. The findings were consistent with, but not conclusive for, an unusual autonomous adrenocortical carcinoma, or a carcinoma developing over a long period of time on a substrate of abnormal hyperplastic adrenal tissue.

1415 ENHANCED MITOCHONDRIAL FUNCTIONS DURING HEPATOCARCINOGENESIS. (E.) Banks, W. L., et al. (Med. Coll, Virginia, Richmond), J. J. Terz and S. S. Higgins. *Proc Soc Exp Biol Med* 138(1):325-329, 1971.

Hepatic mitochondrial functional activities were studied in relation to the administration of the carcinogen, *N*-2-fluorenylacetamide (2-FAA). Male Fischer rats between the ages of 22 and 33 weeks of age were fed either a diet containing carcinogen or were placed in a group maintained on a normal laboratory diet. Rats in both groups were sacrificed and subjected to liver excision at various intervals up to the 51-week termination point. Biochemical tests on the hepatic cells of these excised livers were performed to determine ADP/O, respiratory control ratio (RCR), and phosphorylation rate (PR). It was found that all of the experimental parameters (ADP/O, RCR, and PR) were significantly elevated in the carcinogen-fed rats and the livers were much enlarged due to these elevations. In addition, each liver from 2-FAA-fed animals contained hyperplastic nodules of the type that would develop prior to hepatocarcinogenesis. In a few instances, hepatomas were also found in this group. Since elevation in respiratory

control and phosphorylation rate coincided with liver enlargement, it is suggested that enhanced mitochondrial functional activities were indeed a result of the carcinogen, and that increased mitochondrial efficiency of energy retention may be a property common to early stages of hepatic neoplasia, as well as to other forms of liver damage.

1416 HISTOPATHOLOGY AND ENZYMOPATHOLOGY IN THE RAT CEREBELLUM IN CHEMICAL CARCINOGENESIS. (Rus.) Berezov, T. T. (Acad. Med. Sci., Moscow, U.S.S.R.), S. S. Burobina, V. Z. Gorkin, N. A. Spryshkova and L. Y. Yablonovskaya. *Biull Eksp Biol Med* 72(11):74-76, 1971.

See also:

- \* (Chem); 1269
- \* (Immun); 1390

- 1417 INCIDENCE OF CARCINOMA OF THE CERVIX UTERI.  
(Ger.) Neumann, G. (Pub. Hlth. Dept.  
Stuttgart, Germany). *Arch Gynäk* 210(2):131-149, 1971.

Data on the incidence of cervical carcinoma recorded between April 1969 and March 1970 in the Nordwürttemberg and Südwürttemberg-Hohenzollern districts, including 5.1 million of the population of the southwestern part of West Germany are presented. Of the 643 recorded cases, 227 (35.3%) were in stage zero (carcinoma *in situ*) and 13(2.0%) of the recorded cases were in stage IV (of invasive carcinoma). Of all the recorded cases, 67.9% were ascertained by 21% of the hospitals involved in the campaign and 32% were detected by preventive screening tests. The overall incidence of invasive carcinoma was found to be 15.9 per 100,000 with a peak of 44.2 per 100,000 in the age group 50-55 yr; the incidence of preinvasive tumor was 8.6 per 100,000 with a peak of 25.2 per 100,000 in the 35-40 age group. Histologic proof was achieved in 96.4% of all the detected malignancies. No correlation between morbidity and mortality could be established upon data breakdown according to individual counties. Recording of data on cervical cancer in the two above-mentioned districts is being continued.

- 1418 EPIDEMIOLOGY OF BRONCHIAL CARCINOMA IN A MOUNTAIN REGION. (E.) Gsell, O. R. (Med. U. Polyclin., Basel, Switzerland). *Oncology* 25(5): 410-414, 1971.

Bronchial carcinoma was found in men living in a mountain region of Switzerland free of air pollution, towns or heavy car traffic. The incidence was much lower than that observed in Swiss urban areas (1.5 per 10,000 per yr vs 5 per 10,000 per yr). Ninety-six percent of alpine district men with lung cancer were heavy smokers, primarily of cigars or pipes. The average age at death in cigar smokers with lung cancer is eight yrs higher than that in cigarette smokers (66 yr vs 58 yr). It is concluded that lung cancer is connected not only with cigarette smoking but also with cigar smoking.

- 1419 HISTOPATHOLOGIC CLASSIFICATION AND NATURAL HISTORY OF MALIGNANT TESTIS TUMORS IN NORWAY, 1959-1963. (E.) Miller, A. (Norwegian Radium Hosp., Oslo) and R. Seljelid. *Cancer* 28(4):1054-1062, 1971.

This work is an attempt to produce a simple classification for testis tumors. Data was obtained from the Norwegian Cancer Registry, which provided 314 case histories of patients diagnosed during 1959-1963. Basically, five tumor types were recognized. They are: 1) seminoma, a low-mortality tumor type characterized by uniform large cells resembling spermatogonia; 2) embryonal carcinoma, a fatal tumor which is composed of large pleomorphic cells with amphophilic cytoplasm; 3) teratoma, a random mixture of adult and fetal tissue, which may or may not fatally metastasize; 4) choriocarcinoma, a rare tumor distinguished by both cytotrophoblastic and syncytiotrophoblastic cells; and 5) lymphoma, which affects the reticular tissue of the testis. The average tumor incidence was found to be 3.5

per 100,000 males per year. All tumors are discussed in terms of clinical presentation and diagnosis, location, probability of metastasis, and treatment. In-depth analysis of the relationship of testis maldescent to malignancy is also presented.

- 1420 CARCINOMA OF THE ESOPHAGUS IN SOUTH CAROLINA. (E.) Bates, D. C. (Med. U. South Carolina, Charleston), J. C. Caston, P. O'Brien and S. H. Sandifer. *J S Carolina Med Ass* 67(11):453-456, 1971.

- 1421 CHORIOEPITHELIOMAS IN ALGERIAN WOMEN. (F) Bonafos, M. (Algiers), R. LeCannelier, A. Ouyahia et Laliem. *Med Afrique Noire* 18(7):629-631, 1971.

- 1422 SOME EPIDEMIOLOGICAL CLUES IN THYROID CANCER: TONSILLECTOMY, ACNE, ALLERGY, ETHNICITY. (E.) Bross, I. D. J. (Roswell Park Mem. Inst. Buffalo, N.Y.), K. Shimaoka and J. Tidings. *Arch Intern Med* 128(5):755-760, 1971.

- 1423 THE CHANGING PATTERN OF LEUKEMIA: A SURVEY OF 339 CASES. (E.) Bansal, O. P. (S.N. Med. Coll., Agra, India), V. P. Mital, P. K. Wahal and D. K. Hazra. *Indian J Med Sci* 25(9):590-597, 1971.

- 1424 THE PATTERN OF THE PATHOLOGY OF OVARIAN TUMOURS IN PREGNANCY IN THE SINGAPORE-MALAYSIA REGION. (E.) Sinnathuray, T. A. (Dept. Ob. Gyn., U. Malaya, Kuala Lumpur, Malaysia). *Med J Malaya* 26(1):53-55, 1971.

- 1425 STUDIES IN THE EPIDEMIOLOGY OF MYXOMATOSIS IN CALIFORNIA: IV. THE SUSCEPTIBILITY OF SIX LEPORID SPECIES TO CALIFORNIAN MYXOMA VIRUS AND THE RELATIVE INFECTIVITY OF THEIR TUMORS FOR MOSQUITOES. (E.) Regnery, D. C. (Dept. Biol. Sci., Stanford U., California) and I. D. Marshall. *Amer J Epidem* 94(5):508-513, 1971.

- 1426 STATISTICAL OBSERVATION OF RENAL TUMOR IN THE LAST 6 YEARS AT THE UROLOGICAL CLINIC OF YAMAGUCHI UNIVERSITY HOSPITAL. (Jap.) Kanzaki, Y. (Yamaguchi U. Sch. Med., Japan), S. Kikkawa, T. Koganemaru, T. Kiriya and J. Sakatoku. *Nishinippon J Urology* 33(5):559-69, 1971.

See also:

- \* (Rev): 1211, 1227, 1233, 1234, 1235, 1236, 1237, 1238, 1240  
\* (Phys): 1307  
\* (Viral): 1356



# MISCELLANEOUS

STUDIES OF CELLULAR PROLIFERATION IN HUMAN LEUKEMIA: VII. CYTOKINETIC BEHAVIOR OF PLASTIC CELLS IN A PATIENT WITH RETICULUM SARCOMA IN A LEUKEMIC PHASE. (E.) Ohara, K. (Kettering Inst., New York, N.Y.), J. Fried, J. Dowling, Jr., E. S. Bittar and B. D. Clarkson. *Leukemia* 28(4):862-885, 1971.

Cytokinetic behavior of neoplastic cells was studied in a 22-year-old woman with rapidly progressing disseminated reticulum cell sarcoma (RCS). Shown by the infusion of <sup>3</sup>H-thymidine and autoradiographs that some reticulum (RS) cells matured into monocytoid forms and were unable to divide. The more mature forms showed cytochemical and kinetic differences from normal granulocytes and monocytes. Some cells long-lived. A close correlation with nuclear age and ages of the most primitive RS cells in the marrow was demonstrated. A mean generation time of about 6 days was noted in the labeled RS cells after continuous infusion of <sup>3</sup>H-thymidine; however, that of the whole population was longer. The mean duration of G<sub>1</sub> in the labeled cells was about five days with a minimum of about two days. The duration of M was about two hours, of G<sub>2</sub> about 10 hours, and of S about one day. Small cells had a maximum duration of 20 days. The results for the proliferation of RS cells in a femoral marrow were similar to that of marrow cells. Approximately half of the RS cells were killed by a three day course of arabinosylcytosine (Ara-C); however, within 7 days after withdrawal of the drug the surviving cells were proliferating at almost the same rate as the whole population. Following the Ara-C infusion, the Type I cells in G<sub>1</sub> appeared to mature directly without undergoing any intervening divisions to Type II cells.

BIOCHEMICAL STUDY OF NUCLEI ISOLATED FROM NORMAL LUNG AND FROM LUNG TUMORS: II. NUCLEI OF LOW MOLECULAR WEIGHT. (E.) Yazdi, E. (Univ. Coll. Med., Houston, Texas) and F. Gyorkey. *Cancer Inst* 47(4):765-770, 1971.

Heterogeneity of low-molecular wt RNAs obtained from isolated nuclei of human lung tissue was investigated. Whole nuclear RNA from normal lung and lung tumor tissues was fractionated by centrifugation on sucrose-density gradients. Nuclear RNAs from normal and neoplastic tissues consistently contained a dispersed peak corresponding to the low-molecular wt RNAs with approximate sedimentation coefficients of 16S. Cell nuclei of the lung tissues consistently had at least 6 major groups of low-molecular wt RNAs. Each group detected in normal lung nuclei had a corresponding RNA in each cell type of lung carcinomas. The mobilities on gel electrophoresis of nuclear RNAs from human lung carcinomas were indistinguishable from those in normal lung tissue. The relative amounts of low-molecular wt nuclear RNAs of human lung tissues differed from those of the low-molecular wt RNAs of the Novikoff rat hepatoma. The nucleic acid composition of low-molecular wt nuclear RNAs from normal and neoplastic lung tissues was investigated.

The cytidine monophosphate (CMP) content was lower in the low-molecular wt nuclear RNAs of human normal lung (14.6%) than in those of human liver (25%). Similarly, CMP content was lower in the low-molecular wt nuclear RNAs of rat lung (11%) than in those of rat liver (21%). CMP levels were lower in neoplastic than in normal tissues, while guanosine monophosphate levels were higher in neoplastic than in normal tissues. Adenosine and uridine monophosphate levels in normal and neoplastic tissues were similar.

1429 STUDIES ON PROTEINS OF ANIMAL RIBOSOMES. IX. PROTEINS OF RIBOSOMAL SUBUNITS OF SOME TUMORS CHARACTERIZED BY TWO-DIMENSIONAL POLYACRYLAMIDE GEL ELECTROPHORESIS. (E.) Bielka, H. (German Acad. Sci., Berlin), J. Stahl and H. Welfle. *Arch Geschwulstforsch* 38(2):109-112, 1971.

Two transplantable rat hepatocellular tumors induced by diethylnitrosamine or by dimethylaminoazobenzene, three other rat tumors (Jensen, Yoshida, and Walker), and normal liver tissues were excised and treated to yield free ribosomes. These ribosomes were then purified, lysed, and subjected to a sucrose gradient centrifugation. After protein extracts were isolated from the gradient and dissolved in a solvent, two-dimensional electrophoretic separation was carried out. It was found that total ribosomal proteins of tumors and normal cells could be separated into about 60 spots of varying intensities. Isolated subunits yielded 76 different components upon further electrophoresis. Ribosomes from normal and malignant tissues seemed to be identical with regard to protein composition. These results agree with those of studies on the antigenicity of ribosomes and their proteins from normal rat liver and rat hepatocellular carcinoma.

1430 COMPARATIVE STUDIES OF THE CYTOLOGIC AND METABOLIC CHARACTERISTICS OF C<sub>3</sub>H MOUSE CELLS DURING "SPONTANEOUS" ALTERATION AND NEOPLASTIC CONVERSION *IN VITRO*. (E.) Kieler, J. (Fibiger Lab., Copenhagen, Denmark), J. Moore, B. Biczowa and C. Radzowski. *Acta Path Microbiol Scand A*(79):529-544, 1971.

The cytology, energy metabolism, and growth of four permanent C<sub>3</sub>H mouse cell lines were investigated at different stages of their neoplastic conversion. Primary explants of mixed tissues from 19-day old C<sub>3</sub>H mouse embryos and the lung and spleen of a normal C<sub>3</sub>H adult mouse were used to develop three cell lines. The explants were cultivated in chicken plasma clots and tumorigenicity was confirmed by subcutaneous inoculation into the interscapular region of newborn inbred mice of the C<sub>3</sub>H strain. After 12-16 months of cultivation all three cell lines produced sarcomas in virtually 100% of the newborn mice inoculated. Microscopic examinations showed frequent moderate signs of invasiveness and pulmonary metastases. All cell lines were typical fibroblast-like cultures which at no time could be distinguished from one another by routine microscopy. However, quantitative studies revealed various differences in oxygen uptake, lactate produc-

tion, and glucose consumption in the cell lines. The quantitative cytologic studies failed to reveal any characteristic differences between altered, but non-tumorigenic and tumorigenic cells. However, the possibility that the morphological changes represent an essential part of the process of malignant transformation and that cells in the fourth phase of alteration are malignant was not excluded. The development of new antigenic properties may explain the failure to produce progressive tumor growth in animals of the original donor strain, but the present results indicate that the development of a higher glycolytic capacity may enable the cells to overcome the immunological barrier.

- 1431 FINE STRUCTURE OF CULTURED CELLS AND HERPES-TYPE VIRUS-BEARING FLOATING CELLS FROM TAIWAN NASOPHARYNGEAL CARCINOMAS. (E.) Sugano, H. (Cancer Inst., Tokyo, Japan), M. Takada, H.-C. Chen and S.-M. Tu. *Gann* 10:235-248, 1971.

Eighty-six biopsy specimens from primary nasopharyngeal carcinoma were taken, of which 47 gave rise to cultures showing epithelioid or fibroblastoid growth or both. No virus particles were observed in the cultured cells attached to the glass surface when examined by the electron microscope. On the 52nd day one culture developed floating growth; this cell line was designated as NPC-204. Examination showed that these cells appeared to be a mixed population of plasmoblastoid, lymphoblastoid and reticular cells. Electron microscopy showed herpes-type virus to be present, particularly in degenerating cells, along with crystalline arrays and crystalloid bodies. The presence of herpes-type virus was confirmed by an immunofluorescent study.

- 1432 ALEUTIAN DISEASE WITH POLYCLONAL HYPERGAMMAGLOBULINEMIA OF MINK: HISTOLOGICAL STUDIES IN CORRELATION TO THE GAMMA FRACTION. (E.) Kurata, T. (Fac. Med., Shinshu U., Japan), Y. Yokota, M. Kotani, M. Asano and H. Kawai. *Med J Shinshu Univ* 15(3):153-167, 1970.

Histological studies of Aleutian disease with polyclonal hypergammaglobulinemia of mink are presented. Aleutian disease of mink is characterized by a systemic proliferation of plasma cells with hypergammaglobulinemia which appears to show many features of human multiple myeloma. The study revealed that the higher the gamma-globulin level, the more predominant was the plasma cell proliferation or infiltration of organs. Primary myelofibrosis in the bone marrow of the affected mink was also observed.

- 1433 ELECTRON MICROSCOPIC OBSERVATION ON THE PROLIFERATING MODE OF PLASMA CELLS AND ON CHEDIAK-HIGASHI'S GRANULAR ANOMALY WITH INTERPRETATION FOR ALEUTIAN DISEASE OF MINK. (E.) Asano, M. (Fac. Med., Shinshu U., Japan), Y. Yokota, T. Kurata and I. Kawahara. *Med J Shinshu Univ* 15(3):169-185, 1970.

An ultrastructural study is reported on the proliferating mode of plasma cells and on Chediak-Higashi's granular anomaly with their relationship to Aleutian disease of mink. The electron microscopic studies showed: 1.) the presence of microfibrils in the perivascular areas of the bone marrow; 2.) extramedullary hematopoiesis in the pulp cord of the spleen; 3.) thickening and distortion of the basement membrane with swelling and proliferation of both epithelial and mesangial cells of the kidneys; and 4.) electron dense deposits in the basement membrane of the arterial capillary and parietal epithelium. The microfibrils and the extramedullary hematopoiesis were associated with idiopathic myelofibrosis. Distortion of the basement membrane indicated glomerulonephritis. No plasma cell infiltration was demonstrated in the blastomatous ultrastructure of the various organs.

- 1434 A STUDY OF LEUKEMIC CELL INJURY BY PHYSIC AGENTS. (E.) Miura, M. (Nagoya U. Sch. Med., Japan), K. Kawashima, H. Nishiwaki, M. Kobayashi, A. Morita, R. Ohno, H. Kakizawa, T. Uetani, M. Hirano and K. Yamada. *Cancer Res* 31(10):1451-1456, 1971.

The effects of a hyperthermic and a hypotonic state upon several types of human leukemia cells *in vitro* are reported. It was concluded, using dye exclusion as the criterion, that: acute monocytic leukemia was relatively resistant to both states; acute myeloblastic leukemia cells were sensitive to hyperthermia but resistant to a hypotonic state; acute lymphoblastic leukemia was sensitive to both states. Of chronic lymphatic leukemias studied, two showed a resistance to hyperthermia but were fragile to hypotonic conditions, and the other two were fragile under both conditions. There was no correlation between hyperthermic and osmotic fragility ( $p > 0.05$ ). Where hyperthermic fragility and age of the acute leukemia patient correlated well ( $0.02 < p < 0.05$ ), no such relation existed between osmotic fragility and age of the patient ( $p > 0.05$ ). It was concluded that each leukemic cell type showed characteristic biophysical properties. Factors which may influence these properties as well as the possibility of classifying leukemias according to their biophysical properties were discussed.

- 1435  $\alpha$ -FETOPROTEIN: ITS IMMUNOFLOUORESCENT LOCALIZATION IN HUMAN FETAL LIVER AND HEPATOMA. (E.) Purtilo, D. T. (U. Minnesota Med. Sch., Minnesota) and E. J. Yunis. *Lab Invest* 25(4):291-294, 1971.

An immunofluorescent study for localization of  $\alpha$ -fetoprotein (AFP) in human fetal liver and hepatoma is reported. Sections of 21 human fetuses from 3.5 to 41 weeks gestation, nine hepatomas, two hepatocellular adenomas and one normal adult liver were studied. As a control, immunodiffusion identification of AFP in the patients' serum and tissue homogenate was done. The results showed that AFP was present,



immunofluorescence, in the 3.5 to 32-weeks fetal rats, however, it was not detectable beyond 32 weeks gestation. Diffuse, intense intracytoplasmic AFP was found in nearly all of the fetal hepatomas. Large tumor cells in six of the nine hepatomas tested were AFP-positive. The hepatoma cells and fetal hepatocytes demonstrated almost identical patterns of positivity. The concept that AFP is a foetal embryologic antigen produced in the cytoplasm of the hepatocytes of fetal liver and hepatomas was further supported by the findings of this study.

A NEW ENDOGENOUS INHIBITOR FOR MOUSE MELANOMA CELLS. (E.) Adachi, K. (Oregon Reg. Cancer Res. Ctr., Beaverton), F. Hu and S. Kondo. *Mem Biophys Res Commun* 45(3):742-746, 1971.

This paper describes a new endogenous natural inhibitor of mouse melanoma cells. The inhibitor was extracted from both melanotic and amelanotic B16 mouse melanomas, purified, and found to be 4S cytoplasmic protein. Addition of this extract to melanoma cells in culture caused complete degeneration of the cells within 24-48 hours, suggesting possible mediation of cell death by specific immunity. No additional hormones were required for this action.

HORMONAL EFFECTS ON THYMIDINE KINASE ACTIVITY IN NORMAL RAT ADRENAL AND IN ADRENAL-DEPENDENT ADRENAL CARCINOMA. (E.) Garland, R. (Dept. Biochem., U. British Columbia, Vancouver, Canada), T. Ng and J. F. Richards. *Can J Biochem Physiol* 31(10):1348-1354, 1971.

Studies of experiments were conducted to clarify the hormonal requirements of an adrenal tumor in comparison to those of the normal rat adrenal. Thymidine kinase activity decreased during tumor regression after removal of estrogen from rats with estrogen-dependent adrenocortical carcinomas. The thymidine kinase activity was not altered by administration of growth hormone or adrenocorticotrophic hormone in this tumor. These findings were in contrast to those of the normal rat adrenal in which thymidine kinase activity is independent of the estrogen supply of the host animal. The mechanism remains unknown.

COMPARATIVE ULTRASTRUCTURAL STUDIES ON BIOPSIED SPECIMENS AND CULTURED CELLS OF ACHIE-4 DERIVED FROM LYMPHATIC TISSUE OF A PATIENT WITH HODGKIN'S DISEASE. (E.) Kimura, I. (Aichi Cancer Res. Inst., Osaka, Japan), M. Hoshino and T. O. *Gann* 10:75-87, 1971.

A biopsied lymph node of a 50-year-old man with Hodgkin's disease and *in vitro* cultured cells designated as Achie-4 established from the node were compared in an electron microscopic study. The biopsy material showed small lymphocytes, few histiocytes, a moderate number of mononuclear or

binuclear giant cells, and medium-sized reticulum cells with phagocytosis. The Achie-4 cells showed three distinctive morphologic categories based on size and shape: Type I, small lymphoid cells; Type II, medium sized reticuloid cells; and Type III, multinucleated giant cells. No virus-like particles were observed in 3000 Achie-4 cells examined. The characteristics of each cell type examined, in addition to the possible relationship among cellular elements of the biopsied material, were discussed.

1439 VIRIONS AND CELL ALTERATIONS IN EPIDERMODYSPLASIA VERRUCIFORMIS WITH MALIGNANCY: ELECTRON MICROSCOPIC STUDIES. (E.) Ikuta, F. (Brain Res. Inst., Niigata U., Japan), N. Inomata and T. Kumanishi. *Gann* 10:3-27, 1971.

Epidermodysplasia verruciformis, a chronic human skin disease occasionally followed by carcinoma, was studied in two patients: a 19-year-old male exhibiting waxy, warty, brownish papules, verruca plana-like lesions, and verrucous lesions with papillomatous hyperkeratosis; and a 47-year-old female with verrucous lesions and accompanying liver cirrhosis and chronic gastritis. Morphologic findings of the skin lesions in both cases were fundamentally identical. Light microscopy studies revealed hyperkeratosis of the lesions as well as the presence of large clear epithelial cells which were homogeneous both in the nucleus and in the cytoplasm. Electron microscopic analyses indicated that the cytoplasm of affected cells was homogeneous to the extent that few identifiable organelles were present. Scattered electron-dense fine granules and scattered fibrillar structures were seen, along with diffusely scattered virions. The nuclear membrane was quite irregular in form, and the nuclear chromatin of cells containing virions was aggregated near it. The nucleoplasm itself was replaced by fibrillar material and had numerous virions, either in groups or scattered throughout. When present, nucleoli occasionally contained virions. The presence of elongated rod-like particles was found in both cases, some of which were attached to the virions. When further clinical studies were conducted on the female to determine the effect of the virus on the cirrhosis and gastritis, no relationship was found. In addition, a skin malignancy found when the female was hospitalized was also unrelated to the verrucous virus.

1440 DNA CONSTANCY IN HETEROPLIIDY AND THE STEM LINE THEORY OF TUMORS. (E.) Kraemer, P. M. (Los Alamos Sci. Lab., N.M.), D. F. Petersen and M. A. Van Dilla. *Science* 174(4010):714-717, 1971.

Experiments are reported which suggest that heteroploid cell populations consist of one or more subpopulations, each with a characteristic DNA content per cell and each with a characteristic modal chromosome number. DNA content per cell is apparently constant within a subpopulation, but chromosome number appears to vary. In the study at hand, cellular DNA was measured by high-speed flow microfluorometry in diploid and heter-

oploid cells of human and hamster origin; cells were stained by the fluorescent-Feulgen procedure. Heteroploid cells had higher modes for DNA content and chromosome number than diploid cells. Despite this difference, the variability of DNA content per cell was the same in diploid and heteroploid cells. Mutations causing defects in the chromosomal condensation and kinetochore development systems may cause variable chromosome number without attendant genetic variability.

- 1441 CLONAL ORIGIN OF PHILADELPHIA CHROMOSOME AND CHRONIC MYELOID LEUKAEMIA: EVIDENCE FROM A SEX CHROMOSOME MOSAIC. (E.) Fitzgerald, P. H. (Nelson Hosp., New Zealand), A. F. Pickering and J. R. Eiby. *Brit J Haemat* 21(4):473-480, 1971.

A 69-year-old male patient with chronic myeloid leukemia who exhibited a constitutional XY/XXY sex chromosomal mosaic as determined by cytogenetic studies of lymphocytes cultured with PHA is described. The patient showed normal intelligence and phenotype. During an acute phase of the leukemia a bone marrow aspirate showed the Ph<sup>1</sup> chromosome in cell line 46,XY but not in cell line 47,XXY. By clonal evaluation, two other cell lines were thought to be derived from the 46,XY, Ph<sup>1</sup>-positive line, one of which demonstrated ambiguous features. These results indicate a clonal origin of the Ph<sup>1</sup> chromosome as well as that of chronic myeloid leukemia. It is interesting to note that apparently the 46,XY cells had been replaced by the 46,XY Ph<sup>1</sup>-positive cell line. This was not the case in the 47,XXY cells.

- 1442 DEMONSTRATION OF AN ATPase AT THE CELL SURFACE OF INTACT NORMAL AND NEOPLASTIC HUMAN CELLS IN CULTURE. (E.) Agren, G. (Inst. Med. Chem., U. Uppsala, Sweden), J. Ponten, G. Ronquist and B. Westermark. *J Cell Physiol* 78(2):171-176, 1971.

A sensitive method is given for monitoring an ATPase reaction at the cell surface of intact normal and neoplastic cells in culture. Several of the advantages of this method are: 1) the cells are cultured in a single dish; 2) the cells are firmly attached to the supporting medium throughout the experiment; 3) the incubation medium can easily be separated from the cells at the end of the reaction; 4) there is no diffusion of the surface-located ATPase into the surrounding media; and 5) microscopic observations of the cells can be performed during the reaction if desired. Glia-like cells derived from normal adult brain cells showed a high ATPase activity but cell lines from gliomas were found to have very low activity. A marked decrease in ATPase activity was demonstrated in one SV40 transformed glia line. In general the normal fibroblasts and sarcoma cells had a low activity as compared to the glioma cells.

- 1443 FAMILIAL MEDULLARY THYROID CARCINOMA, PHEOCHROMOCYTOMA, AND PARATHYROID ADENOMA (SIPPLE'S SYNDROME): STUDY OF A KINDRED. (E.) Catala,

W. J. (Natl. Cancer Inst., Bethesda, Md.), K. Engelman, A. S. Ketcham and W. G. Hammond. *Cancer* 28(5):1245-1254, 1971.

A study was made of 14 patients from a kindred, ten of whom had Sipple's syndrome (medullary carcinoma and pheochromocytoma) and six with coexistent parathyroid adenomas or hyperplasia. There was 70% bilateral involvement in pheochromocytoma and 92% in medullary thyroid carcinoma. Chemical or clinical evidence of hyperparathyroidism in two-thirds of the patients was associated with parathyroid adenomas or chief cell hyperplasia. Three of the 14 patients studied died with medullary carcinoma but no mortality was associated with pheochromocytoma. The recommended treatment of Sipple's syndrome was an abdominal exploration with mobilization of both adrenal glands (excision as indicated) and total thyroidectomy with regional lymphadenectomy. A discussion covering clinical features, hereditary pattern and pathogenesis of Sipple's syndrome, with emphasis on awareness of the features of the syndrome, proper management and performance of routine screening tests was given.

- 1444 THE ABSENCE OF A NON-NUCLEOTIDE LINKER IN POLYOMA AND  $\phi$ X174 DNA. (E.) Radloff, R. (Lab. Chem. Biol., California Inst. Tech., Pasadena) and J. Vinograd. *Biochim Biophys Acta* 247:207-219, 1971.

Experiments designed to determine if polyoma DNA contains a non-nucleotide component in the form of a region non-digestible by *E. coli* phosphodiesterase (exonuclease I) were performed.  $\phi$ X174 DNA and polyoma DNA were labeled with <sup>3</sup>H-thymidine and purified. The DNA's were incubated with pancreatic deoxyribonuclease and treated with exonuclease I containing a low level of endonuclease activity (this was considered in evaluating the results). The presence of a single block to exonuclease I in  $\phi$ X174 DNA should have resulted in at least 18% of the counts in total linears in the digest, but only 6.3% of the counts represented total linears and 59% represented acid-soluble mono- and dinucleotides; these results indicate that there was no block to the action of exonuclease I in  $\phi$ X174 DNA. Similar results were found for polyoma DNA.

- 1445 FEMINIZING GONADAL STROMAL TUMORS: ANALYSIS OF THE GRANULOSA-THECA CELL TUMORS OF THE OVARIAN TUMOR REGISTRY. (E.) Novak, E. R. (Johns Hopkins Mem. Hosp., Baltimore, Md.), J. Kutchmeshgi, R. S. Mupas and J. D. Woodruff. *Obstet Gynec* 38(5):701-713, 1971.

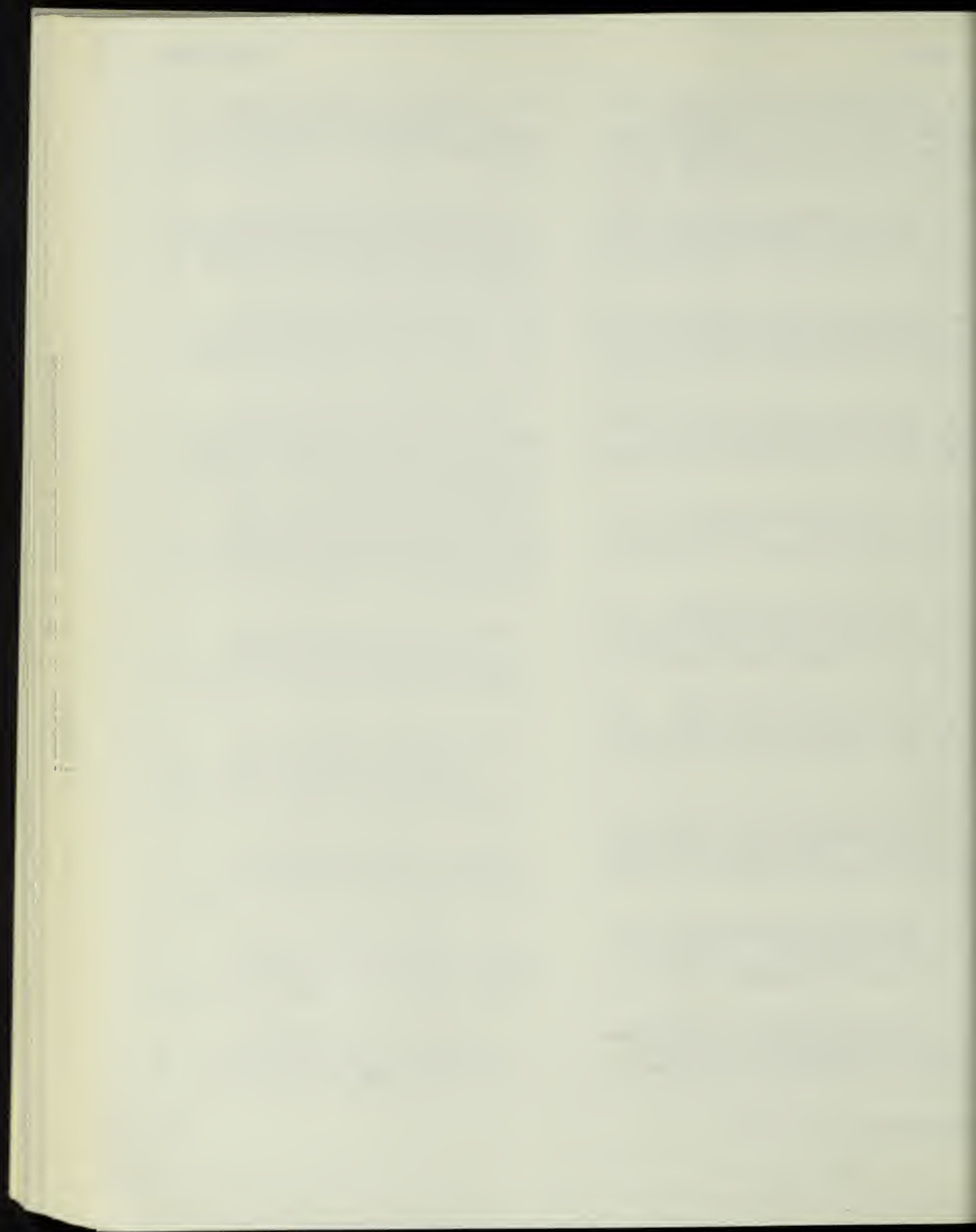


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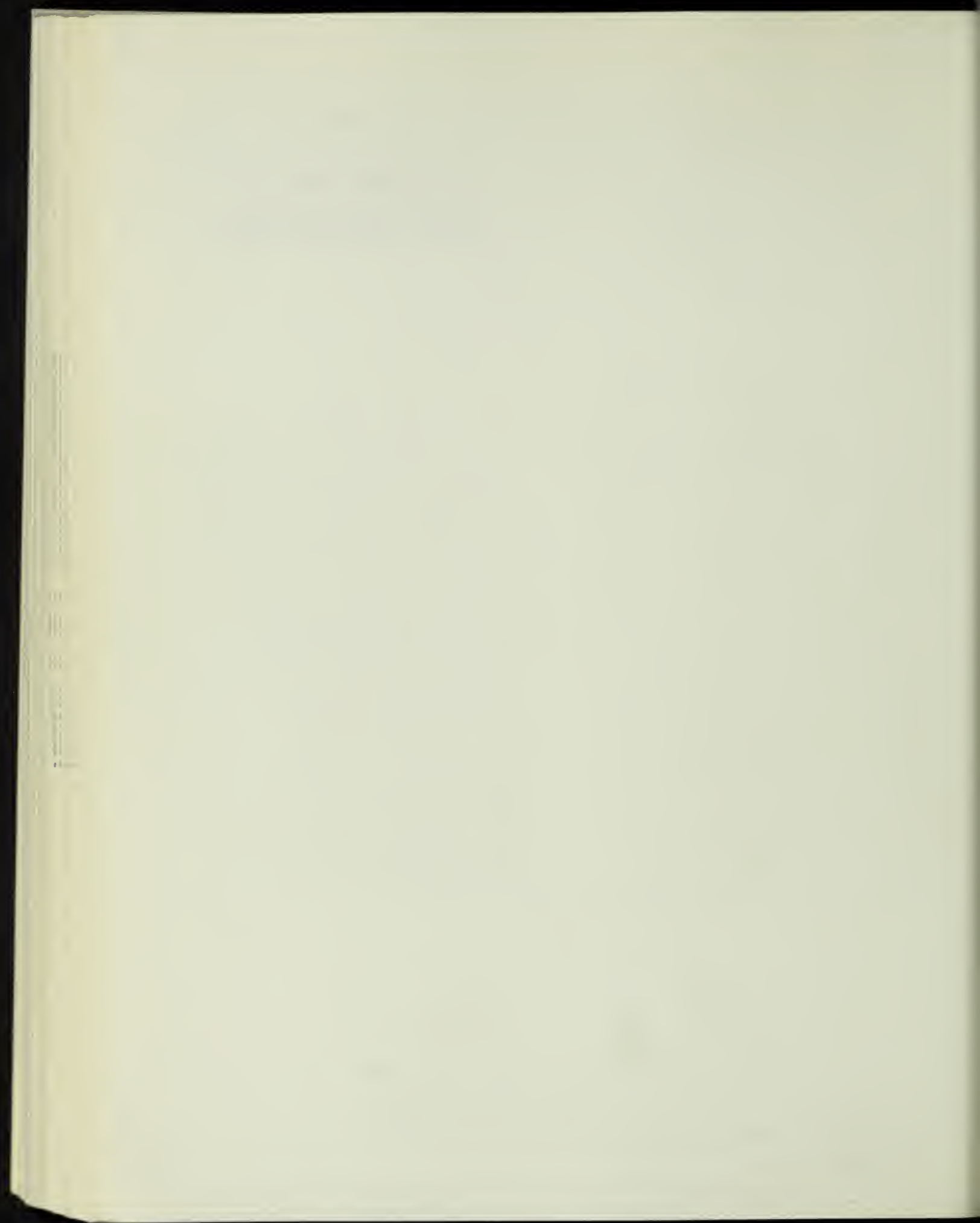
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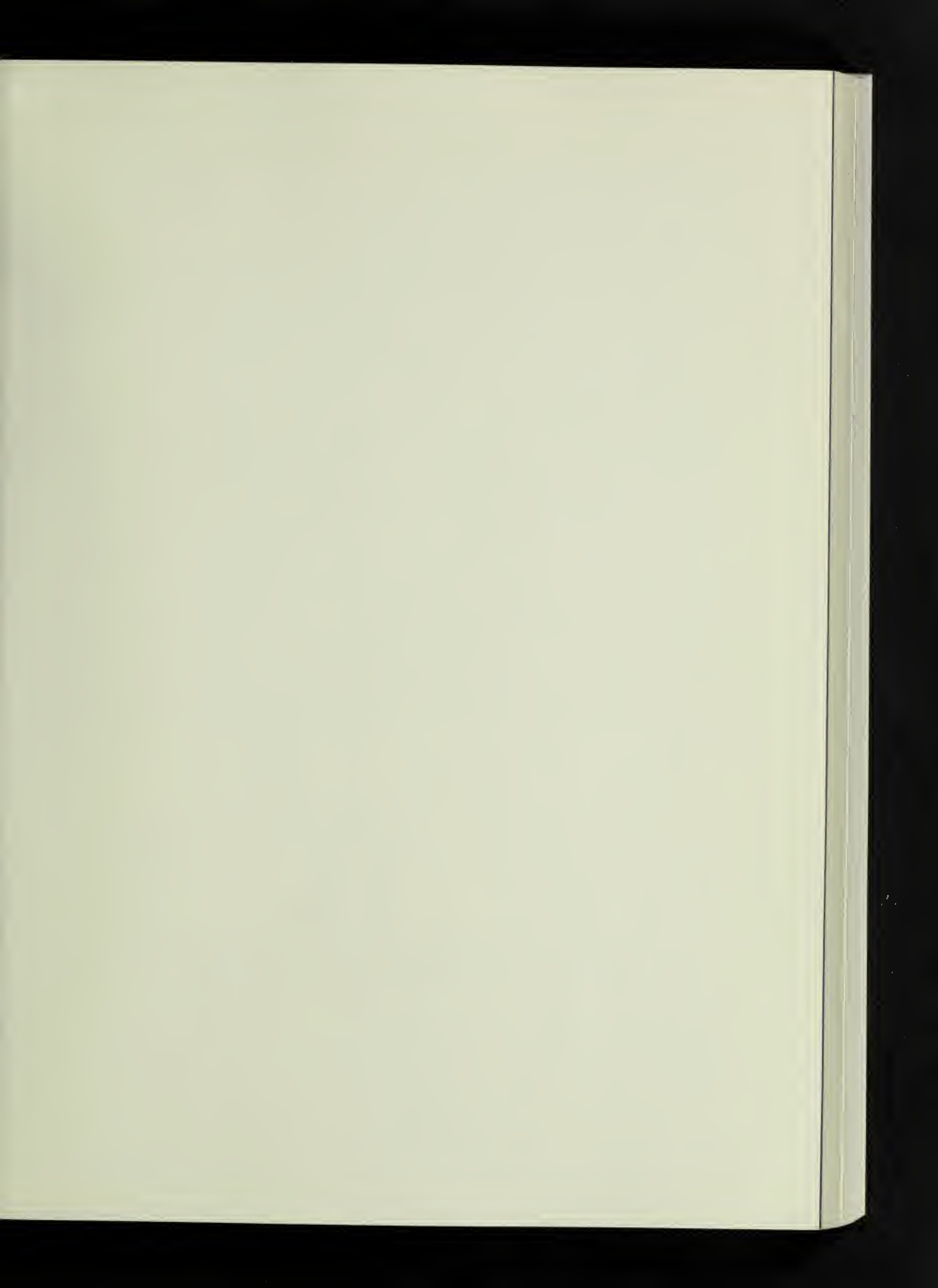
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# **CARCINOGENESIS ABSTRACTS**

**National Cancer Institute**

**U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • National Institutes of Health**





## CARCINOGENESIS ABSTRACTS

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**Editor**

Robert Love, M.D.  
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**Associate Editor**

George P. Studzinski, M.D.  
Jefferson Medical College, Philadelphia

**NCI Staff Consultants**

Elizabeth Weisburger, Ph.D.

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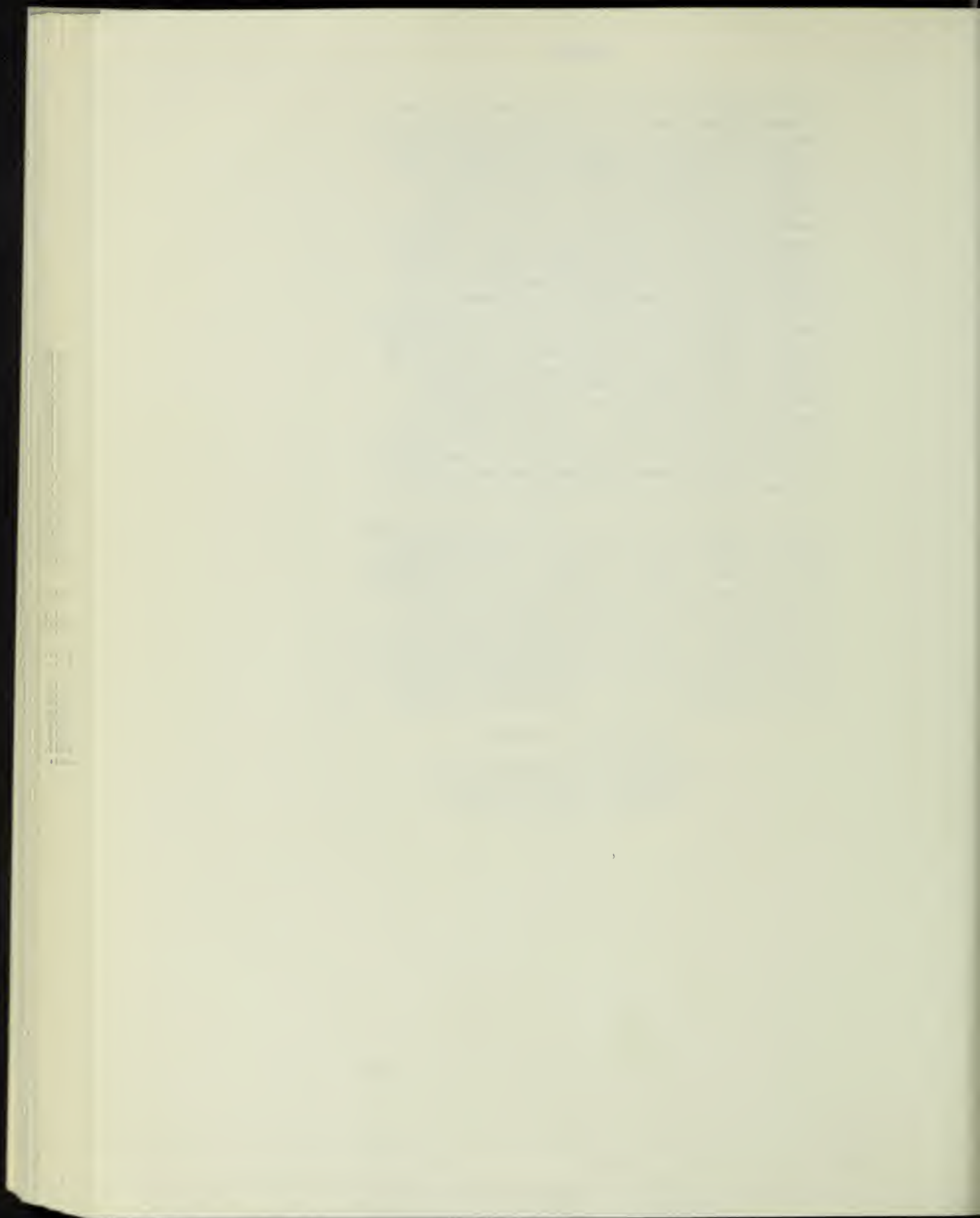


## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred-fifty abstracts and three-hundred-fifty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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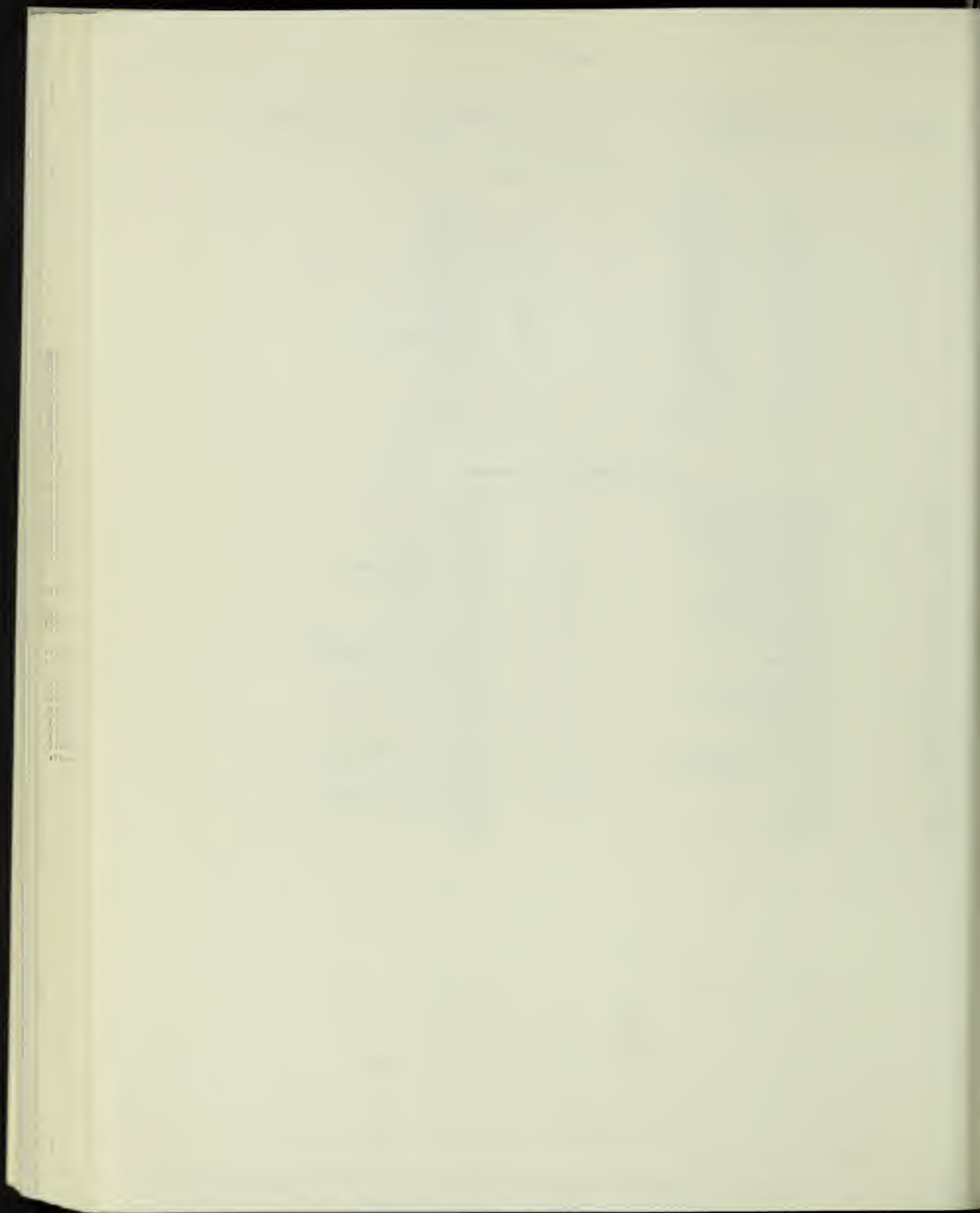
Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

## LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
ln.	Indonesian	Viet.	Vietnamese

## ABBREVIATIONS USED IN ABSTRACTS

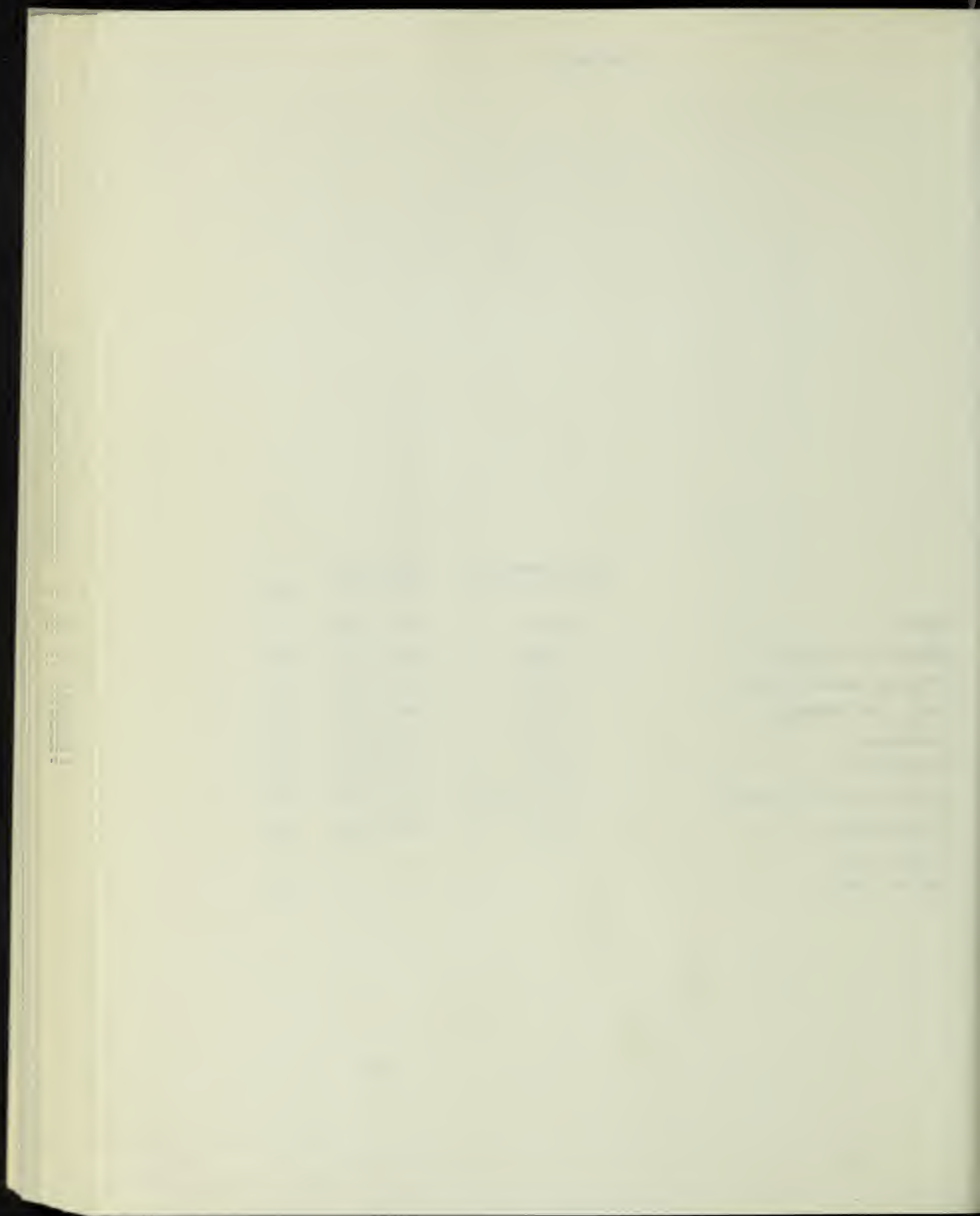
ACTH	adrenocorticotrophic hormone	mC, $\mu$ C	milli-, microcurie(s)
ADP	adenosine diphosphate	mg	milligram(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
BSP	sulfobromophthalein	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram ( $10^{-9}$ )
CNS	central nervous system	pg	picogram ( $10^{-12}$ )
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
$\mu$ g	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	SGOT	serum glutamic-oxalacetic transaminase
kg	kilogram(s)	SGPT	serum glutamic-pyruvic transaminase
LD <sub>50</sub>	median lethal dose(s)	U	unit(s)
LDH	lactic acid dehydrogenase	UV	ultraviolet
m	meter(s)	WBC	white blood cells (leukocytes), white blood count
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
$\mu$ M	micromolar		





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- 1501 SOME ASPECTS OF THE SEARCH FOR A HUMAN MAMMARY TUMOR VIRUS. (E.) Moore, D. H. (Inst. Med. Res., Camden, N.J.), N. H. Sarkar, B. Kramarsky, E. Y. Lasfargues and J. Charney. *Cancer* 28(6): 1415-1424, 1971.

Milk from the inbred Parsi community of Bombay, India, having an unusual cancer-site pattern and a relatively high incidence of breast cancer, was compared with milks from two groups of American women, those with a familial breast cancer association and "controls" with no familial history of breast cancer. Virus-like B-type particles similar to those responsible for transmitting mammary tumors in mice were present in 39% of the Parsis, in 31% of the American donors with a family history of breast cancer, and in 12% of the controls. There was a 100% correlation between the presence of RNA-dependent DNA polymerase and the presence of the virus particles. Finally, human sera from the breast cancer patients were used to neutralize virus which was subsequently inoculated into virus-free, tumor-free assay mice of the strain C57BL. A significant reduction in tumor formation was noted in the mice injected with the cancer sera-neutralized virus as opposed to mice inoculated with virus neutralized with control sera. (63 references)

- 1502 NUTRITIONAL AND DIETARY FACTORS IN NEOPLASTIC DEVELOPMENT. (E.) Shils, M. E. (Mem. Hosp., New York, N.Y.). *Cancer J Clin* 21(6):399-406, 1971.

Studies with laboratory animals on associations between nutrition and tumor development are reviewed. Certain rat studies have shown that the risk of developing tumors is directly and exponentially related to caloric intake; a correlation of tumors with protein intake was also found. Malignant lymphomas have occurred in rats on high protein diets, while tumors in rats with low protein intake were predominantly fibromas and fibrosarcomas. Tumors related to vitamin and mineral deficiencies are discussed, as are modifications of carcinogens by nutrient intake and correlation of dietary deficiencies and tumor growth. Data relating neoplasia to human dietary practices and data on the relation of body weight to the incidence of cancer in man are also reviewed. (71 references)

- 1503 CELL PROLIFERATION AND THE DIFFERENTIAL RESPONSE OF NORMAL AND MALIGNANT TISSUES. (E.) Lamerton, L. F. (Inst. Cancer Res., Sutton, Surrey, England). *Brit J Radiol* 45(531):161-170, 1972.

The selective killing effect of cytotoxic agents by "phase-specific" and "cycle-dependent" action is a major challenge to research in cell kinetics. Bone marrow and intestinal epithelium are used as examples of normal renewal tissue, being vital tissues with a high rate of cell turnover. Treatment of cancer radiation and chemical agents aims at achieving the best differential response between normal and malignant tissue. Response to radiation

treatment by malignant tissue is based on site localization whereas chemotherapy response is dependent upon cell transport systems and the properties of the membranes within the body. Basic cell kinetics are outlined briefly, with discussion of the kinetic activity of cells in response to treatment with methotrexate, dimethylmylenan or radiation. Stem cell responses to therapy are treated in terms of tissue architecture and tissue function. The need to distinguish between "effective" and "potential" tumor stem cells is stressed. Further research into tumor repopulation and change in tumor cell kinetics could provide an avenue by which manipulation of the rate of malignant cell proliferation could be achieved. Value is seen in increasing the integration of radiotherapy and chemotherapy on a clinical basis. (26 references)

- 1504 METALS, LIGANDS, AND CANCER. (E.) Williams, D. R. (Dept. Chem., U. St. Andrews, Scotland). *Chem Rev* 72(3):203-213, 1972.

A review which attempts to highlight additional fields of study for research in coordination chemistry, specifically those fields involving metal complexes for therapeutic cancer research, is presented. Metals, both main group and transition, are discussed in regard to life in general and to human life in particular. Ligand donor groups have been found in many organic species, including amino acids, peptides, hormones, nucleic acids, carboxylic acids, carbohydrates and lipids; they are commonly used in pharmaceuticals, and have been frequently employed to remove metal ions from human tissue. Cancer has reportedly been caused by pure metals such as aluminum, chromium, gold, selenium and zinc; metallic ions and their complexes have been found to be carcinogenic. Some carcinogens can act directly as strong ligands, under either aqueous or nonaqueous conditions, and others react indirectly by metabolizing into strong ligands. Ligand donor groups of known and suspected carcinogens include 2-amino-1-naphthol, benzidine, metabolites of tryptophan, and 8-hydroxyquinoline. It is suggested that malignant cells may use more or stronger ligands than normal cells; ligand deficiencies may also cause cancer. Cancer drugs have been found to be viable ligands; ligand donor groups include triethylenemelamine, aminopterin, 6-mercaptopurine and 5-fluorouracil. Anticancer drugs may be antiviral agents; thus a metallotherapeutic designer may diminish viral activity by metal complexation or may use the virus to direct the toxic ligand into the tumor. It is suggested that tumors in a ligand environment may be susceptible to complexometric therapy. (108 references)

- 1505 TRANSPLACENTAL CHEMICAL CARCINOGENESIS IN MAN. (E.) Miller, R. W. (Natl. Cancer Inst., Bethesda, Md.). *J Nat Cancer Inst* 47(6):1169-1171, 1971.

A report issued in April 1970 indicated that synthetic stilbestrol therapy during pregnancy caused vaginal cancer in the children 14-22 years later; this was

the first time transplacental carcinogenesis was observed in man. Evidence has been found for other prenatal determinants of cancer; evidence includes: 1) congenital cancers which grow large *in utero*; 2) mortality peaks soon after birth; 3) excessive concurrence of certain cancers and congenital malformations; and 4) increase of childhood leukemia related to high maternal age or low birth order. The mode of transmission for prenatal determinants is known for those predeterminants involving germ cells, transplantation and ionizing radiation. Studies of mice showed that stilbestrol can cause cervical cancer and granular cell myeloblastoma as well as vaginal cancer. Other chemicals are thought to be carcinogenic agents during the fetal stage, including aminopterin, immunosuppressive drugs, Dilantin, chloramphenicol, and environmental chemicals other than drugs, such as alkylmercury or heat transfer agents, which damage the embryo by producing malformations. (22 references)

- 1506 SPECIFICATIONS FOR CUTTING OILS WITH SPECIAL REFERENCE TO CARCINOGENICITY. (E.) Catchpole, W. M. (British Petroleum Co. Ltd, Sunbury-on-Thames, England), E. MacMillan and H. Powell. *J Inst Petroleum* 57(557):249-260, 1971.

A study, conducted by the Institute of Petroleum (UK), of the potential carcinogenicity of oils used in industry, particularly those oils used in metal-working operations in which workers' skin is directly exposed to oil, is described. Evidence was found that some oils can cause skin tumors in mice. Suspicion is directed mainly at the polycyclic aromatic hydrocarbons. Other hydrocarbons which are not in themselves carcinogenic may modify the carcinogenic potency of the polycyclic aromatics. Solvent refining reduces the carcinogenicity of oils for mouse skin. In related studies, three time consuming techniques for isolating and estimating the content of benzo(a)pyrene in hydrocarbon mixtures of industrial lubricating oil are compared. However, no satisfactory simple method for setting a specification point to ensure acceptable safety (with respect to carcinogenesis) of oils used in the engineering industry has yet been found. (20 references)

- 1507 THE MALIGNANT CHANGE IN CHRONIC WOUNDS. (E.) Wein, A. J. (Hosp. U. Pennsylvania, Philadelphia), W. P. Graham, III and H. P. Royster. *Industr Med* 41(1):12-14, 1972.

Data on the development of malignant tumors in chronic wounds and unhealing scars are reviewed. The extremities and the face are the most common sites in which such tumors develop. Burn scars, leg ulcers, chronic pilonidal sinuses and fecal or urinary fistulae are among those conditions which may undergo malignant degeneration. Malignant degeneration usually occurs at the site of injury, and usually commences after a latent period of from 20-40 years. The latent period may be reduced to a few weeks if there is a premalignant change in the effected area. (17 references)

- 1508 VIRUSES AND HUMAN CANCER. (E.) Allen, D. W. (Massachusetts Gen. Hosp., Boston) and P. Cole. *New Eng J Med* 286(2):70-82, 1972.

Current ideas related to oncogenic viruses are reviewed. The papova, adeno-, herpes-, and pox viruses--the DNA viruses--are discussed in terms of virus particle morphology, infectivity mechanisms, host ranges, and clinical manifestations. The oncornaviruses--the RNA viruses--are discussed in a similar fashion. It is suggested that current research in both the DNA and RNA viruses be geared to epidemiologic analysis. (104 references)

- 1509 BLOCKING FACTORS IN THE IMMUNE RESPONSE. (E.) Beverly, P. (Natl. Inst. Res., London, England) and E. Simpson. *New Scientist* 52(744):154-156, 1971.

Early links between immunology and cancer research and recent concepts concerning blocking factors in immune response are discussed. The existence of tumor specific antigens raised the question of why tumors were not recognized as "non-self" and rejected by the body's immune systems. Using their colony inhibition technique the Hellströms discovered that an immune response was indeed effected in tumor-bearing animals. They also showed that most human cancer patients had circulating lymphocytes which were immunologically capable of killing their tumor cells *in vitro*, but that serum from these patients, which contained substances termed "blocking factors", would prevent this. This concept was extended by studies in which newborn mice injected with cells from another mouse strain subsequently accepted skin grafts from that strain. Lymphocytes from the tolerant mice, however, killed donor cells *in vitro*; this response could be blocked by serum from the tolerant animals. Similar phenomena have since been variously described, thus contradicting the clonal selection theory of immune tolerance proposed by Burnet. Evidence against the blocking factor theory has consisted of contradictory results from tolerance induction in newborn rats and the ability of tolerant mice to reject skin grafts following the injection of only a few immune lymphocytes. The current interpretation of experimental data favors a blocking mechanism whereby antibody binds to small molecules of antigen. These complexes presumably interfere with killing by sticking to the target cells rather than the lymphocytes, since in experiments in which either the lymphocytes or the target cell were exposed to the complex separately, washed and then mixed, blocking of killing occurred only when the target cells had been preexposed. (No references)

- 1510 IMMUNOLOGY AND MALIGNANT DISEASE. (E.) Klein, E. (Karolinska Inst., Stockholm, Sweden) and A. J. Cochran. *Haematologia* 5(3):179-203, 1971.

Chemical- and virus-induced experimental tumors have different immunological characteristics; while cross reaction is rare in the former case, common cell surface antigens are produced in all tumors induced by the same virus. Tumor associated cell surface antigens (TAA), however, seldom induce absolute resistance in the host. It has been generally observed



that the larger the tumor cell inoculum, the better is the chance of a "take," presumably because by the time the host has achieved a significant immune response, the tumor has attained an unmanageable population size. Work on TAA evolved to the use of *in vitro* systems which have been of great importance in determining the possible viral etiology of tumors, especially human tumors. Several characteristics of TAA suggest that they may be associated with the neoplastic process. Host response to malignancy has been studied and confirmed in humans by utilizing clinical observation and detection of antibodies and lymphoid cells which are reactive with host tumor cells. Although cell-mediated host anti-tumor activity was detectable, in many cases patients still had growing tumors indicating that the immune response was ineffective. The detection of common TAA in tumor groups may not necessarily be indicative of viral etiology, since tumors tend to acquire oncogenic or non-oncogenic agents which then secondarily induce membrane associated antigen. This problem is discussed in relation to Burkitt lymphoma. High titers of Epstein-Barr virus (EBV) have regularly been detected in sera of these patients by membrane immunofluorescence studies. It is virtually certain that EBV causes infectious mononucleosis since only individuals who do not have antibodies to the virus can acquire the disease and antibodies to the virus develop during the course of the illness. EBV may be an etiologic factor in several other diseases, including nasopharyngeal carcinoma and the sarcomatous variety of Hodgkin's disease. It remains to be determined whether EBV can stimulate cell proliferation alone or whether other agents working synergistically are required. (189 references)

- 1511 A SURVEY OF LITERATURE ON DIMETHYLNITROSAMINE AND DIETHYLNITROSAMINE AS CARCINOGENS. (E.) Ma, R. M. (Bur. Foods, Federal Dept. Agric., Washington, D. C.). *FDA by-Lines* 2(3):136-155, 1971.

Literature from the past two decades which is relevant to the subject of dimethyl-nitrosamine and diethylnitrosamine as carcinogens is cited and partially annotated. References are listed according to biologic effects, source, analysis, detection and purification of the compounds and their metabolites. (170 references)

- 1512 PRECANCEROUS STATES "IN VITRO." IMMUNOLOGIC, MORPHOLOGIC AND DYNAMIC MANIFESTATIONS. (Fr.) Bonneau, H. (C.R.A.C.M., Marseilles, France), H. P. Bonneau and D. Robert-Vague. *J Franc Otorhinolaryng* 20(9):971-977, 1971.

Cellular transformation can be induced in a BHK 21 fibroblast strain from newborn hamster kidneys by contact with a nonmodified virus (SV 40 virus, adenovirus), with a virus modified by heat or irradiation (UV, x-rays) or spontaneously after repeated subculture. Morphologic criteria of cellular transformation are: lack of cellular differentiation, basophilia, dense chromatin, altered intercellular relationships (straddling), and loss of adhesion to glass. Immunologic properties, imparted by the action of vi-

rus, and detectable by immunofluorescence, include the appearance of: a viral antigen, T antigen (early ICFA antigen), membrane antigen (surface antigen), and the transplantation antigen (detectable only by tumoral transplantation). Biologic criteria include: cellular growth without certain factors required for normal growth, growth in semisoft agar without nutrients, and reversibility of cellular transformation. Four distinct stages of cancerous cellular transformation have been identified. Stage IA requires the presence of mucopolysaccharide, collagen, and insulin in medium; stage IB no longer requires collagen or insulin in the medium; stage IIA requires the presence of adenine; stage IIB cells grow even without adenine. The first two stages correspond to precancerous states and the last two are malignant transformations. The described morphologic, biologic and immunologic changes indicate only a possible precancerous transformation which can be detected only by transplantation of *in vitro* modified cells. While malignant transformed cells produce a tumor which kills the animal by constant metastasizing growth, precancerous cells cause non metastasizing local tumors which can disappear under certain conditions. (No references)

- 1513 ON THE CARCINOGENICITY OF CYTOSTATIC SUBSTANCES. (Ger.) Hartwich, G. (Med. Clin., U. Erlangen-Nuremberg, Germany). *Med Klin* 66(43):1433-1434, 1971.

Examples of radiation and chemically-induced carcinogenesis are given illustrating the role of cytostatic substances in teratogenesis, mutagenesis and carcinogenesis. Malignant tumors (local sarcomas, and sarcomas and carcinomas in different organs) were induced by ten of 12 different alkylating agents investigated by Druckrey et al. In groups treated with alkylating agents, the malignant tumor incidence was 11-44%, as compared to an incidence of 6% in the control group; no prevailing organotropy could be revealed. Antimetabolites and antibiotics showed no carcinogenic effects except for the antibiotic mitomycin C. The tumor-inducing effect of azathioprine and amethopterin was shown and actinomycin S was found to be carcinogenic for mice. The high degree of heterogeneity and spontaneity of the tumors observed does not permit establishment of definite dose-effect relations. The increased number of tumors, which would occur spontaneously within certain limits of incidence, is attributed to the immunosuppressive action of cytostatic substances. Because of the long induction periods required, the carcinogenicity of cytostatic substances in man cannot yet be ascertained. (4 references)

- 1514 EFFECT OF THE CELL CYCLE ON CARCINOGENESIS (E.) Warwick, G. P. (Chester Beatty Res. Inst., London, England). *Fed Proc* 30(6):1760-1765, 1971.

The role of cell proliferation in cancer initiation is discussed using examples from the areas of chemical, radiation, and viral carcinogenesis. There

is evidence to suggest that cells may differ in their response to carcinogens depending on their stage in the cell cycle when the carcinogen is introduced. The increased sensitivity of the newborn and regenerating adult mammalian liver to the carcinogenic action of certain chemicals or to radiation supports this concept. For example, in a recent experiment urethan was administered as a single dose to adult B6AF<sub>1</sub> mice at different times after partial hepatectomy: 4-5 hours, at an early prereplicative period; 17-18 hours, during the late prereplicative period; 31-33 hours, shortly before the onset of extensive DNA duplication; and 46 hours, before the peak of mitosis. The hepatoma incidence showed a clear-cut relationship between the timing of urethan treatment in relation to prior hepatectomy. After 13 months, 10, 68, 42, and 77% of the male animals bore at least one hepatoma compared with 3% among untreated males, 6% in those treated only with urethan, and 19% following partial hepatectomy alone. If replicating cells prove to be more vulnerable targets than resting cells for chemical carcinogens in general, then more attention must be given to age factors in carcinogenesis and to situations in which excess cell division is induced as a result of malnutrition, disease conditions and other trauma. (78 references)

- 1515 LOBULAR CARCINOMA *IN SITU* OF THE MAMMARY GLAND: HISTOGENESIS, GROWTH, TRANSFORMATION INTO INFILTRATIVE CARCINOMA. (Ger.) Hamperl, H. (Bonn U., Inst. Pathology, Germany). *Dtsch Med Wochr* 96(41):1585-1588, 1971.

The development of lobular carcinoma *in situ* of the mammary gland is attributed to the proliferation of Paget-like cells derived from the myo-epithelium. Growth first occurs by apposition through merging of single foci and expansion later occurs by displacement and substitution of the normal epithelium. As opposed to cervical carcinoma *in situ*, the mammary gland carcinoma *in situ* rarely develops into infiltrative carcinoma. Other types of mammary gland tumors, i.e., mucous, medullar and verruciform carcinoma, are unrelated to the lobular form and, therefore, are unlikely to be related to lobular carcinoma *in situ*. (13 references)

- 1516 THE HISTOCOMPATIBILITY SYSTEMS. (E.) Snell, G. D. (Jackson Lab., Bar Harbor, Me.). *Transplantation Proc* 3(3):1133-1138, 1971.

Cell membrane bound alloantigens are currently demonstrated by three methods: (1.) the use of tumor or skin, or less commonly marrow or other tissue transplants, in appropriately designated inbred strains or segregating generations; (2.) blood typing; (3.) study of alloantigens of nucleated cells of the blood or lymphoid organs by a cytotoxic technique requiring alloantibody and complement. These three methods are used to classify histocompatibility loci; the question whether or not the method of classification used re-

sults in distinct locus groupings is discussed. The so-called histocompatibility genes are those which determine the acceptance or rejection of transplants; the end products of these genes are alloantigens localized in the cell membrane and thus are vulnerable to the immune defenses of the graft recipient. These genes may be part of a family of gene loci either directly or indirectly concerned with histocompatibility. This larger group of loci is referred to as "cell membrane alloantigen determining loci" (CMAD loci). Cell membrane bound alloantigens can be demonstrated by three methods, and antigens are accordingly classified as to their method of identification. One standardized system for classifying and naming CMAD loci is detailed. Evidence bearing on the question of the distinctiveness of the CMAD loci in this system is discussed. Evidently, histocompatibility loci show great diversity with respect both to tissue distribution of their end products and to different arrangements of the end products on the cell surface. Loci demonstrated through an effect on histocompatibility (*H*-loci, in the classification system) may represent a rather distinct group. Methods used to demonstrate anti-*H* antibodies by hemagglutination may not be entirely valid. It is also suggested that the glycoprotein coating found over cell membranes may mask *H*-antigens under some conditions. (35 references)

- 1517 THE BIOCHEMISTRY OF NORMAL AND LEUKEMIC LEUKOCYTES: IV. ENZYMES OF LEUKEMIC CELLS OF THE GRANULOCYTE SYSTEM. (Pol.) Sznajd, J. (Acad. Med., Cracow, Poland), J. Lisiewicz, W. Pajdak and J. Naskalski. *Preg Lek* 28(7):496-499, 1971.

Differences in the activities of the enzymes which metabolize nucleic acids and carbohydrates in normal and in myeloid leukemic granulocytes are reviewed. Leukemic cells show decreased cellular glycogenesis and decreased uridine diphosphoglucose, pyrophosphorylase, phosphoglucomutase and glycogen synthetase activities by comparison with normal granulocytes. Hexokinase, phosphofructokinase, and lactate dehydrogenase activities of the Embden-Meyerhoff cycle are also comparatively depressed in leukemic cells. Enhanced activities of the pentose phosphate cycle enzymes are, however, characteristic of leukemic granulocytes. Decreased thymidine phosphorylase, and increased dihydro-orotase, orotic acid dehydrogenase and DNA polymerase activities are characteristic of the nucleic acid metabolism enzymes of the leukemic leukocytes. Increased acid and decreased alkaline phosphatase levels are observed in chronic myeloid leukemia, while acute myeloid leukemia presents opposite values. Proteolytic enzyme activities are higher in chronic myeloid leukemia and lower in acute myeloid leukemia than in normal granulocytes. (33 references.)

- 1518 THE PIONEERS IN THE STUDY OF CARCINOGENESIS. (E.) Wescott, W. B. (U. Oregon Dent. Sch., Portland). *Bull Hist Dent* 19(2):1-11, 1971. (No references)



- 1519 CONNUBIAL CANCER: COINCIDENCE VS CONTAGION. (E.) Marshall, S. (Berkeley, Calif.). *JAMA* 218(2):1831-1832, 1971. (3 references)
- 1520 WHAT CAUSES CANCER ON THE FARM? (E.) Anonymous. *Med World News* 13(2):424, 1972. (No references)
- 1521 FIBRIN AND CANCER. (E.) Anonymous. *Brit Med J* (5788):641-642, 1971. (14 references)
- 1522 IMMUNITY AND NEOPLASMS. (E.) Durocher, J. (Washington, D.C.). *Arch Intern Med* 129(1):143-144, 1972. (12 references)
- 1523 DESMOPLASTIC VARIETY OF MEDULLOBLASTOMA: HISTOGENETIC CONSIDERATIONS. (It.) Pollice, L. (Inst. Anat. Hist. Path., Bari U., Italy). *Acta Neurol (Napoli)* 26(3):294-296, 1971. (18 references)
- 1524 CYLINDROMA OF THE UTERINE CERVIX WITH PERITONEAL METASTASES: REPORT OF A CASE AND REVIEW OF THE LITERATURE. (E.) de la Maza, L. M. (Boston City Hosp., Mass.) B. A. Thayer and F. Naeim. *Amer J Obstet Gynec* 112(1):121-125, 1972. (16 references)
- 1525 CHROMOSOMAL ABERRATIONS IN BLOOD DISEASES. (Fr.) Catti, A. (Hosp. Cantonal U., Lausanne, Switzerland). *Schweiz Med Wschr* 101:1646-1649, 1971. (63 references)
- 1526 THE PRESENT PROBLEM OF PROSTATE CARCINOMA. (Ger.) Hohbach, M. (Path. Inst., U. Saar, Homburg, Germany) and G. Dhom. *Munchen Med Wehr* 114(2):45-54, 1971. (53 references)
- 1527 CARCINOID AND ADENOID CYSTIC CARCINOMA OF THE BRONCHUS. (E.) Toole, A. L. (Yale-New Haven Med. Ctr., Conn.) and H. Stern. *Ann Thorac Surg* 13(1):63-81, 1972. (172 references)
- 1528 THE AETIOLOGY AND PATHOGENESIS OF THE MALIGNANT TUMOURS OF THE LIVER. (E.) Hoensch, H. (Med. Clin., U. Erlangen-Nuremberg, Germany). *Digestion* 5(1):58-63, 1972. (19 references)
- 1529 LEUKEMIA--DISTURBANCE OF REGULATION? (E.) Anonymous. *JAMA* 219(6):746-747, 1972. (5 references)
- 1530 III. NEOPLASIA: INTRODUCTION AND OVERVIEW. (E.) Steer, A. (Atomic Bomb Casualty Commission, Hiroshima, Japan). *Hum Path* 2(4):501-503, 1971. (12 references)

- 1531 DOMINANT-LETHAL EFFECTS OF CYCLOHEXYLAMINE IN C57BI/Fe MICE. (E.) Petersen, K. W. (Dept. Hlth., Educ. Welfare, Washington, D.C.), M. S. Legator and F. H. J. Figge. *Mutat Res* 14(1):126-129, 1971.

Male C57 BI/Fe mice (20-25 g), 12 weeks of age, were divided into three groups of ten mice each. The mice of one group were given i.p. injections of cyclohexylamine (CHA) in saline (adjusted to pH 7.2 with 0.1 N HCl) at a dose of 100 mg/kg daily for five days. A saline solution of triethylenemelamine (TEM), the positive control compound, was administered to another group for five consecutive days at a dose of 0.05 mg/kg. Mice in the third group were given injections of 0.5 ml of saline. Immediately after the last injection, each male was caged separately with three female mice (C57 BI/Fe) for one week. Two additional weekly matings were made. Twelve days after the end of the last day of mating, the uterine contents were examined for viable implants, dead implants and late fetal deaths. The percentage of dead implants in the TEM-treated group showed the normal decline through the third week. With CHA treatment, the dead implants increased from 13.3% the first week to 15.6% the second week and to 18% the third week; dead implants from the saline treated control mice averaged 4.8% during the three weeks.

- 1532 RENAL TUMORS AND OTHER LESIONS IN RATS FOLLOWING A SINGLE INTRAVENOUS INJECTION OF DAUNOMYCIN. (E.) Sternberg, S. S. (Sloan-Kettering Inst., New York, N.Y.), F. S. Philips and A. P. Cronin. *Cancer Res* 32(5):1029-1036, 1972.

The effects of daunomycin, an antibiotic known to have cytotoxic and pathologic effects, were studied on virgin female Sprague-Dawley rats weighing 120 to 166 g. Groups of 20 rats were given a single i.v. injection in the tail vein of: 20, 10, or 5 mg daunomycin/kg body wt or 0.9% saline. The rats were sacrificed after six months if debilitated, or if they had externally apparent tumors, or after one year; those found dead were not included in the results. Of the 20 rats receiving 20 mg daunomycin/kg 18 died; the other two were killed at day 51 and found to have severe chronic glomerulonephritis. Of the group receiving 10 mg/kg 14 were killed, with the other six being found dead; in the group given 5 mg/kg 19 were killed and one died. In the 33 rats available for pathologic study from the groups given 5 or 10 mg/kg 16 were found to have 27 tumors. Single tumors were found in five of 20 controls; none were renal or genital tract tumors. Kidney adenocarcinomas were seen in two daunomycin-treated rats, with tumors closely resembling in appearance the clear-cell human kidney carcinomas. Renal adenomas were found in five rats and renal cysts in two; seven rats had genital tumors and seven had mammary tumors. All rats having kidney tumors and cysts had chronic glomerulonephritis with severe lesions involving most glomeruli; the glomeruli affected were diffusely fibrotic and many tubules were dilated and cystic. Evidence of hyperparathyroidism secondary to chronic renal disease, as manifested by hyperplasia of the parathyroid glands, metastatic calcification in the kidneys and stomach,

and bone disease, was found in five of six rats given 10 mg daunomycin/kg. It is postulated that daunomycin has a unique effect in that chronic renal disease and renal tumorigenesis are found to be associated.

- 1533 EPOXIDES AS MICROSOMAL METABOLITES OF POLYCYCLIC HYDROCARBONS. (E.) Grover, P. L. (Chester Beatty Res. Inst., London, England), A. Hewer, and P. Sims. *FEBS Letters* 18(1):76-80, 1971.

In an attempt to demonstrate that epoxides are involved in the metabolism of polycyclic hydrocarbons, rats were pretreated with 3-methylcholanthrene and then killed. The livers were excised and a liver microsomal fraction was obtained. These microsomes were mixed with tritiated phenanthrene, benz(a)anthracene or dibenz(a,h)anthracene, after which the mixture was extracted, treated with unlabeled K-region epoxide, and subjected to alumina-column chromatography. It was found that the specific activities of the radioactive epoxides isolated from the microsomal incubations of phenanthrene or benz(a)anthracene did not fall on repeated crystallization with the K-region epoxides. This indicates that the epoxides formed with these two hydrocarbons are most probably the K-region derivatives. The site of oxidation of dibenz(a,h)anthracene has not yet been determined. It is concluded that the initial step in the microsomal oxidation of aromatic double bonds *in vitro* is the formation of an epoxide; under appropriate conditions the epoxide can be converted into the corresponding dihydrodiol, phenol, or glutathione derivatives.

- 1534 EFFECTS OF D-GLUCOSAMINE, D-MANNOSAMINE, AND 2-DEOXY-D-GLUCOSE ON THE ULTRASTRUCTURE OF ASCITES TUMOR CELLS *IN VITRO*. (E.) Molnar, Z. (Dept. Path., U. Chicago, Ill.) and J. G. Bekesi. *Cancer Res* 32(2):380-389, 1972.

Ehrlich ascites carcinoma and sarcoma 180 ascites tumor cells exposed to amino sugars were studied by means of light and electron microscopy. Addition of D-glucosamine or D-mannosamine to the incubation medium caused severe cytoplasmic and nuclear changes. The earliest changes, seen after incubation for 15 minutes, included vacuolization of the cytoplasm and separation of the electron-lucent filamentous parts of the nucleolonema and nucleolar vacuole at the periphery of the nucleolus. As the time of incubation increased, vacuolization of the cytoplasm increased gradually, accompanied by refraction of the cytoplasm around the nucleus. After complete extrusion of its electron-lucent components, the nucleolus became condensed. At the end of three hr of incubation, 95% of the tumor cells had pycnotic, polymorphic, or disintegrating nuclei, and the nucleoli in nearly all the cells examined consisted almost exclusively of the compacted, granular, electron-dense nucleolonema. After four hr, most tumor cells exhibited various degrees of disintegration. Incubation of these tumor cell lines for four hr with 2-deoxyglucose resulted in no significant structural alteration in the ascites tumor cells.



1535 TRANSFORMATION OF HAMSTER CELLS *IN VITRO* BY POLYCYCLIC HYDROCARBONS WITHOUT CYTOTOXICITY. (E.) DiPaolo, J. A. (Nat'l. Cancer Inst., Bethesda, Md.), P. J. Donovan and R. L. Nelson. *Proc Nat Acad Sci USA* 68(12):2958-2961, 1971.

Two flavones, 7,8-benzoflavone (7,8-BzF1) and 5,6-benzoflavone (5,6-BzF1), and benz(a)anthracene (BzA) were studied to determine their effects on the cloning efficiency of Syrian hamster embryo cells and their ability to enhance the transformation of these embryo cells by benzo(a)pyrene (BzP) or 3-methylcholanthrene (MCA). Five hundred two day cultured cells from secondary cultures of hamster embryo cells were plated in two ml of medium in Petri dishes containing a 24 hr culture of feeder layer of  $6 \times 10^4$  irradiated hamster cells. After 24 hr, solutions of 7,8-BzF1, 5,6-BzF1 or BzA were added to the cultures. The next day (48 hr after the nonirradiated hamster cells had been plated), carcinogen was added (BzP 1 or 5  $\mu\text{g/ml}$ ; MCA 2.5  $\mu\text{g/ml}$ ). Some of the plates were given two additional treatments with the protective agents (7,8-BzF1, 5,6-BzF1, BzA) at 48-hr intervals. The medium was not changed during the course of the experiment. When several concentrations of 7,8-BzF1, 5,6-BzF1, or BzA (1 to 5  $\mu\text{g/ml}$ ) were added to hamster embryo cells, the cloning efficiency was unaffected except by 5,6-BzF1 at a concentration of 5  $\mu\text{g/ml}$ . Treatment of cells with either low, high, or multiple doses of 7,8-BzF1 before the addition of either BzP or MCA raised the cloning efficiency above that obtained with the carcinogen only, to a frequency approaching that of control cells treated with medium only. The greatest enhancement of cloning efficiency (13.6% vs 13.7% for controls) was achieved when treatment with 5  $\mu\text{g/ml}$  7,8-BzF1 preceded treatment with 1  $\mu\text{g/ml}$  BzP. Similar enhanced cloning efficiency was seen in MCA-treated cells pretreated with 7,8-BzF1 and in BzP- or MCA-treated cells pretreated with 5,6-BzF1 or BzA. Over all, enhancement was higher with BzA and BzP than with any other combination of "protective agent" and carcinogen. Enhancement of transformation with MCA was maximum with a single treatment of 10  $\mu\text{g/ml}$  BzA, and exceeded the results obtained with all other "protective agents". These results indicate that it is possible to dissociate the transforming from the toxic metabolic properties of BzP and MCA.

1536 DNA REPAIR INHIBITION: A POSSIBLE MECHANISM OF ACTION OF CO-CARCINOGENS. (E.) Gaudin, D. (U. Alabama Sch. Med. Birmingham), R. S. Gregg and K. L. Yielding. *Biochem Biophys Res Commun* 45(3):630-636, 1971.

A variety of compounds which are chemically diverse, but have the common property of being co-carcinogens in different experimental situations, were examined for their ability to inhibit uptake of  $^3\text{H}$ -thymidine by UV-irradiated normal human lymphocytes in an *in vitro* assay system. Incubation was carried out for two hr; in addition to cells and  $^3\text{H}$ -thymidine, the assay system included hydroxyurea to reduce background incorporation as a result of ordinary DNA synthesis. Water-insoluble inhibitors were dissolved in dimethylsulfoxide and added to the incubation

mixture. Co-carcinogens tested (and concentrations required to produce 50% inhibition of repair replication) were: croton oil (0.005%), Tween 80 (0.002%), Span 80 (0.01%), Arlacel A (0.01%), vitamin A alcohol ( $1.7 \times 10^{-5}\text{M}$ ), diethylstilbestrol ( $1.3 \times 10^{-5}\text{M}$ ), estradiol ( $5 \times 10^{-5}\text{M}$ ), progesterone ( $8 \times 10^{-6}\text{M}$ ), testosterone ( $2 \times 10^{-5}\text{M}$ ), 7-hydroxyacetylaminofluorene ( $7 \times 10^{-6}\text{M}$ ), and azobenzene ( $4 \times 10^{-5}\text{M}$ ). All tested co-carcinogens could inhibit repair to different extents, 7-hydroxyacetylaminofluorene being the most potent and the detergents (Tween 80, Span 89, Arlacel A) the least potent. It was concluded that inhibition of DNA repair may be an important mechanism in the action of co-carcinogens.

1537 TRANSFORMATION OF MAMMALIAN CELLS BY CRUDE HISTONES. (E.) Latner, A. L. (Royal Victoria Infirm., Newcastle Upon Tyne, England) and E. Longstaff. *Brit J Cancer* 25(2):280-283, 1971.

Monolayer cultures of BHK21 hamster cells were grown to confluence and given 100  $\mu\text{g/ml}$  histone derived from calf thymus or rat liver. Control cultures were either maintained without treatment or were subjected to various concentrations of polylysine and polyarginine. It was found that histone-treated cultures showed a marked tendency towards centripetal aggregation and multi-layering, calf thymus-derived histone cells aggregated at a rate of 56% and rat liver-derived histone aggregated cells at a 77% rate. On the other hand polylysine and polyarginine were found to be toxic to the cultures at relatively low concentrations. It is speculated that changes in cell morphology and behavior produced by the histones reflect some premalignant changes in the cells. The occurrence of large, irregular multinucleate cells resulting from the histone treatment possibly supports this hypothesis. However, it is certain that these observations were not due solely to the cationic nature of the histone, since polylysine and polyarginine have similar characteristics but failed to maintain cell viability.

1538 SYNTHESIS OF RNA AND NUCLEAR PROTEINS IN EARLY REGENERATING RAT LIVERS EXPOSED TO BERYLLIUM. (E.) Marcotte, J. (Fac. Med., U. Montreal, Quebec, Canada) and H. P. Witschi. *Res Commun Chem Path Pharm* 3(1):97-104, 1972.

Male Wistar rats were partially hepatectomized, and immediately thereafter were injected i.v. with beryllium. Studies done 2, 4, 6, and 12 hr. postinjection included measurement of labelled orotic acid incorporation, determination of RNA polymerase activity, quantitation of labelled leucine incorporation, and measurement of acylation of histones. It was found that no difference existed between test and control rats in any of the experimental parameters at any of the sampling times. It is postulated, therefore, that beryllium could be involved in interfering with the regulation of cell metabolism at the level of chromatin. Such interference would block new transcription of the genome but would leave already-active enzymes intact and unaltered.

- 1539 MYCOTOXINS AND THEIR ROLE IN ONCOGENESIS, WITH SPECIAL REFERENCE TO BLOOD DISEASES. (E.) Aleksandrowicz, J. (Med. Acad., Cracow, Poland) and B. Smyk. *Pol Med Sci History Bull* 14(1):25-30, 1971.

The class *Fungi imperfecti* produces metabolites known as mycotoxins, which are pathogenic for both cold- and warm-blooded vertebrates. To determine if such mycotoxins are harmful to humans, a classification of fungi was carried out on molds obtained from the environments (homes, foods, etc.) of 51 healthy individuals and of 65 patients suffering from a variety of cancers including leukemia, hepatoma, and neoplasms of the digestive tract and reproductive systems. *Aspergillus flavus* was found in 40% of the patient environments and in 9.8% of the control environments; *Penicillium meleagrinum* was found in 58% of the patient foods and homes, but in only 19.6% of the control foods and homes. *Cladosporium herbarum*, *Penicillium turbatum*, and *Fusarium sporotrichioides* were somewhat less frequent in both groups, while *Aspergillus niger* was observed in the environment of 13.4% of the patients and 23.5% of the controls. In addition to this data, epidemiologic correlations were found when the data was analyzed as to tumors in married couples, familial tumors, tumors in certain households, streets and districts showing high tumor incidence, and farms where both humans and animals had tumors.

- 1540 EFFECTS OF POSTTREATMENT ON SINGLE-STRAND BREAKS IN DNA OF *HAEMOPHILUS INFLUENZAE* EXPOSED TO NITROSOGUANIDINE AND METHYL METHANESULFONATE. (E.) Kimball, R. F. (Oak Ridge Natl. Lab., Tenn.), M. Liu and J. K. Setlow. *Mutat Res* 13(4):289-295, 1971.

Several strains of the bacteria *Haemophilus influenzae* were subjected to either methyl methanesulfonate (MMS) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and incubated at either 37° or 0° C. Such treatment caused single-stranded breaks in the DNA chain; these breaks and their repair were measured by radioactive labelling techniques. At low survival levels, it was found that the major effect of incubation at 37° C was breakdown rather than repair. Despite this breakdown there was a consistent but small gain in amount of higher molecular weight material, probably representing actual rejoining of the molecular breakages. At 0° C, however, no more than a small amount of breakdown and little if any change in average molecular weight or in amount of high molecular weight material was noted. Interestingly, derivative DB117, a strain experiencing lethal effects when subjected to MMS or MNNG, also demonstrated repair at 37° C. The results fail to show any relation between single-stranded breaks and the decrease in survival resulting from posttreatment holding at 0° C, or between the ability to repair breaks and the difference in sensitivity between various strains of *Haemophilus influenzae*.

- 1541 STRUCTURE AND TUMOR-PROMOTING ACTIVITY OF ANTHRALIN (1,8-DIHYDROXY-9-ANTHRONE) AND RELATED COMPOUNDS. (E.) Segal, A. (New York U. Med. Ctr., New York), C. Katz and B. L. Van Duuren. *J Med Chem* 14(12):1152-1154, 1971.

Anthrakinone, used to treat psoriasis and related skin diseases, was studied to clarify its structure, transformation products and to assay it and related compounds for tumor-promoting ability on skin of female ICR/Ha Swiss mice. Spectroscopic analysis (infrared (IR) and nuclear magnetic resonance (NMR)) revealed that when anthralin remained in the dark at room temperature or in solution in methanol or dimethylketone it existed in the semiquinone form, 1,8-dihydroxy-9-anthrone. The dimer structure formed from anthralin in dimethylketone was identified by NMR spectroscopy to be 1,6,7,12,18,21-hexahydroxy-5,12:6,11-di-o-[a,e]cyclooctene. Anthralin (80 µg/0.1 ml acetone), anthralin dimer (80 µg/0.1 ml) and three related compounds (1,8-dihydroxynaphthalene 60 µg/0.1 ml; anthrone 70 µg/0.1 ml; and 1,8-dihydroxy-anthraquinone 170 µg/0.1 ml) were tested for tumor promoting activity. A single dose of the initiating agent, 7,12-dimethylbenz(a)anthracene (20 µg/0.1 ml) was applied topically to the interscapular region and was followed two wk later by thrice weekly applications of the promoting agent for the duration of the experiment (490 days).

- 1542 HISTOPATHOLOGY OF RENAL LIPOMATOUS TUMORS IN RATS TREATED WITH THE "NATURAL" PRODUCTS, PYRROLIZIDINE ALKALOIDS AND  $\alpha$ ,  $\beta$ -UNSATURATED ALDEHYDES. (E.) Schoental, R. (Med. Res. Council Lab., Carshalton, England), G. C. Hard and S. Gibbard. *J Nat Cancer Inst* 47(5):1037-44, 1971.

The histopathology of six renal lipomatous tumors arising in rats treated with "natural" products was investigated. Test products included: pyrrolizidine alkaloids from *Heliotropium supinum*, *Amsinckia intermedia* and pure retrorsine; 5-hydroxymethylfurfural; 3,4,5-trimethoxycinnamaldehyde; products of incense smoke; and  $\alpha$ , $\beta$ -unsaturated aldehydes. Grossly, some of the tumors produced were whitish elevations on the kidney surface; others caused hemorrhaging into the peritoneal cavity. Two of the latter group had cystic appendages which extended into the peritoneal cavity. The most striking microscopic feature was the presence of areas of mature fat cells intermingled with smaller areas of marked cellularity and cystic spaces. The tumors resembled "spontaneously" occurring tumors usually classified as liposarcoma and lipomatous hamartoma. The largest of the six tumors was classified as a liposarcoma but the remaining five have been classified as "lipomatous renal tumor" while awaiting further investigation for a more complete classification.

- 1543 METHYLENE-BIS-ORTHO-CHLOROANILINE (MOCA): EVALUATION OF HAZARDS AND EXPOSURE CONTROL. (E.) Linch, A. L. (E. I. Du Pont de Nemours & Co.,



Deepwater, New Jersey), G. B. O'Connor, J. R. Barnes, A. S. Killian, Jr. and W. E. Neeld, Jr. *Amer Ind Hyg Ass J* 32(12):802-819, 1971.

Medical records of 209 employees exposed to 4,4'-methylene-bis (2-chloroaniline) (MOCA) over a 16 yr period were examined to determine whether any significant physiological differences or health effects had developed between members of this group and a statistically equivalent unexposed group. Although MOCA is strongly tumorigenic in rats, no evidence was found that MOCA is tumorigenic in man. Data obtained from urine analysis and air analysis showed definite exposure and absorption of MOCA with degradation in the body dependent on each individual's metabolic system. Skin absorption from direct contact was concluded to be the major source of absorption.

- 1544 ENVIRONMENTAL NITROSO COMPOUNDS: REACTION OF NITRITE WITH CREATINE AND CREATININE. (E.) Archer, M. C. (Dept. Nutr. Food Sci., Massachusetts Inst. Tech., Cambridge), S. D. Clark, J. E. Thilly and S. R. Tannenbaum. *Science* 174(4016):1341-1343, 1971.

Creatine reacts with nitrite under acid conditions to produce N-nitrososarcosine, which has been shown to induce cancer of the esophagus in the rat. Creatinine, the end product of creatine metabolism *in vivo*, reacts with acidified nitrite to produce either creatinine-5-oxime or 1-methylhydantoin-5-oxime depending on reaction conditions. The oximes are of undetermined toxicity. It remains to be determined whether these reactions actually take place in foods or in the mammalian stomach, and their significance in the incidence of human cancer must be evaluated.

- 1545 ONCOGENICITY OF 6-HYDROXYTESTOSTERONE,  $\Delta^3,5$ -CHOLESTADIEN-7-ONE AND  $\Delta^4$ -CHOLESTEN-3,6-DIONE. (Ger.) Güttner, J. (Central Inst. Microbiol. Exp. Ther., Jena, Germany), G. Bruns, W. Zschesche and M. Horn. *Arch Geschwulstforsch* 38(1):10-14, 1971.

Oncogenicity of 6-hydroxytestosterone,  $\Delta^3,5$ -cholestadien-7-one, and  $\Delta^4$ -cholesten-3,6-dione was studied in AB/Jena inbred mice following a s.c. injection at birth and at ten days of age. Each substance was dissolved in olive or sesame oil and administered at a dose of 1.0 mg. In 166 mice given olive oil, no fibrosarcomas developed at the injection site; five malignant tumors developed in these mice at sites other than the injection site. In 156 mice given 6-hydroxytestosterone no tumors developed at the injection site and ten malignant tumors developed at other sites. In 120 mice given  $\Delta^3,5$ -cholestadien-7-one, four fibrosarcomas developed at the injection site and nine malignant tumors developed at other sites. In 172 mice given  $\Delta^4$ -cholesten-3,6-dione, 24 fibrosarcomas developed at the injection site and 44 malignant tumors developed at other sites. Fibrosarcomas prevailed at the injection site while tumors of the lymphoreticular system and of the breast con-

stituted the bulk of the distant malignancies. The assumed relationship between increased 6-hydroxytestosterone and postcirrhotic liver carcinoma could not be confirmed by this *in vivo* study.

- 1546 EFFECTS OF PROGESTERONE, OVARECTOMY AND ADRENALECTOMY ON MAMMARY TUMOURS INDUCED BY 7,12-DIMETHYLBENZ(A)ANTHRACENE IN SPRAGUE-DAWLEY RATS. (E.) Jabara, A. G. (Dept. Path., U. Melbourne, Australia) and A. G. Harcourt. *Pathology* 3(3):209-214, 1971.

Noninbred Sprague-Dawley virgin rats (80) were divided randomly into four equal groups. Groups 1 and 2 underwent adrenalectomy and groups 3 and 4 were subjected to adrenalectomy and ovariectomy. All groups were fed intragastrically a single dose of 7,12-dimethylbenz(a)anthracene to induce mammary tumor formation. Following surgery and carcinogen administration only groups 2 and 4 received progesterone injections. The experiment was conducted over a 28-week period. Evaluation of the data showed that mammary tumors developed in groups 1 and 2, but not in groups 3 and 4, even when continuous partial hormone replacement was carried out. Adrenalectomy did not significantly affect tumor induction time, tumor multiplicity, or the number of neoplasms per rat; tumor locations, growth behavior, and morphologic tumor types which developed were also unaffected. In the presence of progesterone adrenalectomy had no significant effect on multiplicity of tumors, their locations, or the histologic neoplastic types which developed; however, tumor incidence was increased. It is concluded that while progesterone enhances the production of dimethylbenz(a)anthracene-induced mammary tumors in the rat, its presence does not appear to be essential for the induction of mammary tumorigenesis by this carcinogen.

- 1547 ZINC INDUCTION OF TESTICULAR TERATOMAS IN JAPANESE QUAIL (*COTURNIX COTURNIX JAPONICA*) AFTER PHOTOPERIODIC STIMULATION OF TESTIS. (E.) Guthrie, J. (Southampton Gen. Hosp., England). *Brit J Cancer* 25(2):311-314, 1971.

Experiments were conducted to determine whether Japanese quail testes, which grow rapidly during lengthening light periods, were susceptible to teratoma induction by means of metallic salts. Seventy quail, which had been kept in light exposure conditions of two hours of light to ten hours of dark (2L:10D) were given increasing daily light periods (4L:8D and 16L:8D). The testis of birds subjected to increased light periods were enlarged by comparison to testis of birds subjected to the 2L:10D photoperiod. After three weeks in the increased photoperiods, 65 quail were given injections of zinc chloride solution into both testes (0.001 or 0.0006 g of 5 or 3% solutions/single testis). Fifteen injected quail died within 12-24 hours; two teratomas were found in the testes of the remaining 50 birds. Both teratomas occurred in the right testis.

- 1548 THE INDUCTION OF HYPERPLASTIC GROWTH IN *Datura stramonium* BY A THERMOSTABLE ENDO-TOXIN FROM *Agrobacterium tumefaciens*. (Fr.) Savulescu, A. (Cantacuzino Inst., Bucharest, Rumania), L. Mesrobianu, A. Popescu and D. Movileanu. *Ann Inst Pasteur* 121:405-412, 1971.

The inoculation of thermostable endotoxin extracts from the B6, the 6, and the 26 strains of *Agrobacterium tumefaciens* to *Datura stramonium* resulted in 38.9 to 50.8 cases out of 100 of the production of neoplasms. The inoculation of endotoxin extracts from *Salmonella typhi* resulted in the production of neoplasms in *Datura stramonium* in an average of 12 cases out of 100. Control tests performed with bacterial suspensions of *A. tumefaciens* produced neoplasms in 100% of cases. Neoplasms induced by endotoxins from the B6 and 26 strain of *A. tumefaciens* present different morphologic aspects between the 18th and the 30th days post-inoculation in the form of proliferating tumors, developed surface tumors or necrotic tumoral tissues. The growths produced by endotoxins from *Salmonella* and *Proteus* bacteria resembled those from *A. tumefaciens* endotoxins, which produced typical cauliflower-shaped tumors without necroses. Tumors in all cases first appeared on the 10th day following inoculation. Histologic examination of the tumoral tissues disclosed that the property of inducing tissue hyperplasia in *Datura stramonium* is a nonspecific property of the endotoxins and that the biologic phenomena induced are probably independent of their serologic specificity. The difference between the tumors produced by endotoxins studied appears to be only quantitative. Experimental tumor induction shows two phenomena: the production of new tissue masses induced by endotoxins which can also be induced by the injection of attenuated bacteria; and the maintenance of hyperplastic proliferation without the help of exogenous growth hormones.

- 1549 THE INTERACTION BETWEEN SMALL MOLECULES AND NUCLEIC ACIDS STUDIED BY CIRCULAR DICHROISM. (E.) Kaneko, M. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan) and C. Nagata. *Chem-Biol Interact* 3(6):459-468, 1971.

The optical properties of aromatic hydrocarbons and quinolines which were reported as intercalated between DNA base pairs at low binding ratios were studied to determine if a monomeric dye bound to an asymmetric site is responsible for induced optical activity. Calf thymus DNA was exposed to one of six chemicals: benzo(a)pyrene (3,4-BP), pyrene, 4-nitroquinoline 1-oxide (4-NQO), proflavine or acridine orange. The reacted DNA-hydrocarbon solutions were measured by spectrometry for circular dichroism (CD) and for absorption spectra. It was found that pyrene, 3,4-BP and 4-NQO all exhibited a positive or a negative band in the region of the absorption spectra for the complexes when bound to DNA. The 4-NQO, however, had a negative band position coincident with a different spectrum. The CD spectra for these four hydrocarbons had vibrational structures coinciding with the absorption spectra, indicating that the extrinsic Cotton effect was involved. DNA- and RNA-proflavine

complexes were also studied. It was determined by varying temperature and salt concentration that stacking due to dye-dye interaction could occur, inducing a new type of Cotton effect; this new Cotton effect was also noted in DNA- and RNA-acridine orange complexes and in complexes with single-stranded DNA obtained by dilution denaturation at neutral pH. It was concluded that the molecular planes of the aromatic hydrocarbons and quinolines are stacked parallel to the planes of the DNA bases, and that such dye-dye interaction stacking could help maintain the helical structure of even single-stranded DNA, allowing optical activity of the molecule.

- 1550 EXPERIMENTAL INVESTIGATION INTO THE CARCINOGENIC ACTION OF *PENICILLIUM CAMEMBERTI* VAR. *CANDIDUM*. (Ger.) Gibel, W. (German Acad. Sci., Berlin), K. Wegner and G. P. Wildner. *Arch Geschwulstforsch* 38(1):1-6, 1971.

The carcinogenicity of *Penicillium camemberti* var. *candidum* III C 3 on Wistar rats was studied. Suspensions with high mycelium contents were administered through a stomach tube or s.c. in three weekly 0.5 ml doses. Rats treated perorally and s.c. survived an average of over 518 and 399 days, resp. Organ damage and tumor probably associated with the substance administered were observed in rats surviving six months. Fatty change, cell necrosis, granulomas and slight hepatitis were revealed in the liver. Swollen Kupffer cells were characteristic; swollen tubular epithelium showing moderate pyelonephritis in some cases was found in kidneys. Strongly damaged spleen tissue, hypersplenomegaly with ascites, and extramedullary hemopoiesis with reticulum hyperplasia were revealed. Hyperkeratosis was revealed in the renal ampulla. One hepatocellular carcinoma, one spleen sarcoma, one bile duct adenoma, one mammary fibroadenoma, one local epithelial hyperplasia and one hyperkeratosis were found in 17 intragastrically treated rats. Four retroperitoneal sarcomas, one undifferentiated sarcoma, and one immature-cell mixed leukemia were identified in 13 subcutaneously treated rats. Systematic investigations may have resulted in a higher leukemia incidence. No pathologic variations were observed in the control group except for one fibroadenoma. The carcinogenic and leukemogenic effects observed here, possibly caused by mycotoxins, should be studied in other strains of *P. camemberti* and *P. roqueforti*.

- 1551 ISOZYMES IN THE LIVER FROM MICE GIVEN HEPATOCARCINOGEN AND FROM TUMOR-BEARING MICE. (E.) Yanagi, S. (Fac. Med., Kyushu U., Japan), T. Kamiya, Y. Ikehara, and H. Endo. *Cann* 62(4):283-291, 1971.

It has been noted that isozyme patterns of some glycolytic enzymes in hepatoma cases differ from the isozyme patterns of normal liver. These are especially characterized by changes in aldolase and pyruvate kinase levels, where an increase of muscle-type isozyme is accompanied by a concomitant decrease in the liver-type isozyme. To study this phenomenon,



male mice of strain CF#1 were divided into groups: those living under normal conditions and those living under the experimental conditions of either Ehrlich ascites tumor cell inoculation or N,N'-2,7-fluorenylene-bisacetamide (FAA) administered in the diet. After various periods of time, the mice were sacrificed and their livers excised. It was found that mouse muscle pyruvate kinase was neutralized almost completely by anti-rat muscle pyruvate kinase serum and that about 90% of the pyruvate kinase from Ehrlich ascites cells was neutralized by the antiserum. These results indicate that muscle-type pyruvate kinase in the livers and tumors of the mice was present. Enzyme activities were measured and it was discovered that muscle-type activities of aldolase and pyruvate kinase in mice livers was increased both by inoculation of Ehrlich ascites tumor cells and by administration of the carcinogen FAA. Isoelectric resolutions on all those groups revealed that the increased muscle-type pyruvate kinase was a mixture of several enzyme species, one of them having an isoelectric point consistent with the muscle pyruvate kinase, and two others having an isoelectric point intermediate between those of liver-type and muscle-type pyruvate kinases.

- 1552 STRUCTURAL AND MICROCIRCULATORY ALTERATIONS IN THE RAT LIVER FOLLOWING INTERMITTENT ADMINISTRATION OF ALPHA-NAPHTHYLISOTHIOCYANATE (ANIT) FOR 12 MONTHS. (Ger.) Stefenelli, N. (Vienna U., Austria), J. H. Holzner, H. Pointner and L. Stockinger. *Virchow Arch Path Anat* 353(4):302-311, 1971.

Chronic intermittent treatment of rats with  $\alpha$ -naphthylisothiocyanate (ANIT) was used to study the development of connective tissue neoplasia and its effect upon liver structure, microcirculation and the related blood supply of damaged parenchymal tissue. Rats were given a total of 100 mg/kg of ANIT p.o. within a seven-day period; the dose was repeated at 40 day intervals for 12 months. Necrotic foci associated with decreased ATPase and acid phosphatase activities were observed within the hepatic lobule. These decreased enzyme activities, which were observed two to three days after the first treatment period, returned to normal within 50 days. Periportal connective tissue proliferation as well as a narrowing of the bile ducts were observed following three to four series of treatments. Dedifferentiated proliferating epithelial cell populations of the bile canaliculi were seen at the ultrastructural level. These cells contained a few organelles and also contained large amounts of free ribosomes. Typical liver cells containing a large number of mitochondria and well-developed endoplasmic membrane systems with a few lysosomes were scattered among the dedifferentiated cells. No neoplastic tissue could be found within the lobule. A fine granulation of the liver surface was observed six to eight months after the experiment was begun. No ascites formation was detected. Further alterations appeared to depend on the continued administration of ANIT. Microcirculatory alterations included enlargement of the periportal lymph vessels and a decrease in the amount of periportal sinusoids; sinusoids appeared to be characterized by an enhanced arterial blood supply and by a pulsating blood reflex towards the portal

area. Structural alterations were seen mainly in the sinusoid segments and small veins immediately preceding their opening into the larger veins. These alterations were thought to be insufficient to influence the development of the other lesions. No progress was seen in the above alterations within two months following the last administration of ANIT.

- 1553 ORGANOTROPY OF N-2-FLUORENYLACETAMID (2-ACETYLAMINOFLUORENE) CONCERNING AUDITORY MEATUS TUMORS IN TWO DIFFERENT STRAINS OF RATS. (E.) Polyzonis, M. (Theagenion Cancer Inst., Thessalonika, Greece). *Path Europ* 6(3):208-216, 1971.

The incidence of tumors of the auditory meatus induced by 2-acetylaminofluorene (AAF) was studied in two strains of rats. One strain (Marshal) showed a high incidence of liver tumors (94.1% in males, 37.5% in females) and a low incidence of mammary tumors (6.2% in females); the other strain (Buffalo) showed a high incidence of mammary tumors (63.4% in females) and a low incidence of liver tumors in females (64.7% in males, 9.7% in females). Auditory tumors, consisting of cysts, papillomas, adenomas and squamous carcinomas, were seen only in the high mammary tumor Buffalo strain, especially in the males. No other skin tumors were seen. There was no apparent relationship between age, sex or strain and the type of auditory tumor induced by AAF. Since a small, ovoid, relatively undifferentiated cell type was seen in all the auditory tumors, it was suggested that this cell type may be the target of the AAF. Tumors of the sebaceous glands of the auditory meatus were found only in Buffalo rats and were more frequent in males than in females. It was thought that the tumorigenesis of the auditory meatus sebaceous glands and of the mammary glands was controlled by a similar set of factors, possibly hormonal in nature.

- 1554 EFFECT OF LITHOCHOLIC ACID ON DL-ETHIONINE CARCINOGENESIS IN RAT LIVER. (E.) Hiasa, Y. (Dept. Path., Nara Med. U., Japan), Y. Konishi, Y. Kamamoto, T. Watanabe, and N. Ito. *Gann* 62(4):239-245 (and Plates XLV-L), 1971.

Lithocholic acid in small quantities is an important metabolite of cholesterol in man and in experimental animals; in large quantities it can cause liver cirrhosis, ductular proliferation, and gallstone formation. The present work investigates the reaction of lithocholic acid when administered with the hepatocarcinogenic agent DL-ethionine. Male Wistar rats were divided into groups and were fed either a basal diet alone, or a basal diet supplemented with either or both DL-ethionine and lithocholic acid. After 30 to 34 weeks, the rats were fasted for 18 hours and then sacrificed. Gross anatomical observations, light microscopy analysis, and electron microscopic studies were performed on the liver tissue at autopsy. It was found that the basal diet alone caused no clinical abnormalities of the liver, but all other diets, including the chemicals, did. Lithocholic acid alone caused a retardation in body weight gain.

In addition, the liver cells experienced an infiltration of oval cells with concomitant atrophy of the parenchymal cells; fibrosis and a few bile duct stones were also found. DL-Ethionine caused the surface of the liver to become rough and nodular. Hyperplasia with instances of hepato-cellular carcinoma also occurred, except at low concentrations. When lithocholic acid and DL-ethionine were administered simultaneously, it was found that the liver developed rough, large nodules, indicating hyperplasia. Hepatocarcinoma was also found, but only in cases of highest DL-ethionine concentration. This work suggests that liver fibrosis was induced by lithocholic acid alone, with the resulting cirrhotic changes being reduced by treatment with DL-ethionine. It is not known, however, whether there is any relationship between chemical alteration of bile composition and development of hyperplastic nodules and fibrosis.

- 1555 MALIGNANCY IN NATURAL AND EXPERIMENTAL HEPATIC CYSTS: EXPERIMENTS WITH AFLATOXIN IN RATS AND THE MALIGNANT TRANSFORMATION OF CYSTS IN HUMAN LIVERS. (E.) Cruickshank, A. H. (Dept. Path., U., Liverpool, England) and S. M. Sparshott. *J Path* 104(3):185-190 (incl. Plates LXV-LXXI), 1971.

The following study was performed to determine similarities between human liver growths and chemically induced cancers in rats. Twelve male 4-week old rats were given a diet containing aflatoxin, a known liver carcinogen. The rats were maintained on the toxic meal for 14 weeks, after which they were given normal laboratory food. At various times over a two-year period all of the rats either died or were sacrificed. It was discovered upon autopsy that every animal had hepatic tumors, some of which had spread to lymph nodes, peritoneum, and lungs. All the hepatic tumors contained cysts progressing in stages from benign to poorly differentiated malignant cells. Most of the tumors could be classified as carcinomas of the biliary epithelium. This experimental work was then related to four human case histories of patients suffering from liver cystadenosarcomas. The human cysts are believed to be the result of congenital malformations of the bile ducts, known as v. Meyenburg complexes. These cysts appear to start with benign cells but develop into a tumor of low malignancy that becomes progressively more malignant. In comparison, then, the rat and human cell disorders are similar. It has been postulated that contamination of food with aflatoxin or analogous chemicals could be a cause of the malignant progression of v. Meyenburg complexes; the authors, however, discount this possibility.

- 1556 BIOCONCENTRATION AND BIOTRANSFER OF AFLATOXIN. (E.) Nevins, M. P. (Dept. Microbiol., Colorado St. U., Ft. Collins) and D. W. Grant. *Bull Envir Contam Toxicol* 6(6):552-558, 1971.

Toxigenic strains of *Aspergillus flavus*, which excrete aflatoxins, were isolated from manure, stockpiled in a commercial feedlot, and used in a laboratory-simulated food chain. It was shown that housefly

maggots fed on aflatoxin-contaminated manure contained aflatoxin in their biomass. When fed to rainbow trout these maggots produced acute liver pathology consistent with severe aflatoxicosis. These results suggested the possibility of biotransfer and biomagnification of aflatoxin through natural sources, such as improperly harvested and stored grains and seeds.

- 1557 EFFECT OF AFLATOXINS ON RAT LIVER REGENERATION. (E.) Gershbein, L. L. (Northwest Inst. Med. Res., Chicago, Ill.) and A. F. Pedroso. *Acta Hepatosplen* 18(6):453-459, 1971.

The results of experiments to show the effect of aflatoxins on rat liver regeneration are reported. Holtzman rats were partially hepatectomized (two-thirds of the liver removed), individually caged and given water and aflatoxin-supplemented diet ad lib. At 10.5 days the rats were killed, the liver was removed and dried, and liver regeneration was observed. It was found that 2.0 ppm aflatoxin depressed liver regeneration in males but showed no effect on females (with or without ovariectomy). Regeneration was inhibited in animals of either sex when 4.0 or 5.0 ppm was given. Immature male rats were given s.c. injection of the toxin (600 µg/kg daily) postoperatively while large adult males received 140 µg/kg daily for three or seven days postoperatively. The few survivors showed a marked depression of the regenerative process when they were sacrificed at nine days. Crystallin aflatoxin G<sub>1</sub> fed at 3.0 or 3.3 ppm or a culture product of *Aspergillus flavus* containing four aflatoxins with 44% B<sub>1</sub> aflatoxin given at 0.5 ppm showed no effect. Intact young males used as controls underwent no significant changes after comparable treatment with B<sub>1</sub>. It was concluded that partially hepatectomized rats show a greater sensitivity to aflatoxin than the intact animal and that no definite difference is noted according to sex.

- 1558 DIET AND AFLATOXIN B<sub>1</sub> TOXICITY IN RATS. (E.) Rogers, A. E. (Dept. Nutr. Food Sci., Massachusetts Inst. Tech., Cambridge) and P. M. Newberne. *Toxic Appl Pharmacol* 20(1):113-121, 1971.

Sprague-Dawley and Fischer male weanling rats were maintained on either an adequate diet or a marginally lipotrope-deficient diet. Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>) was administered i.p. one or more times or by gastric intubation (i.g. route); in addition, some rats were given protective compounds i.g. (including mercaptoethylamine (MEA), vitamin K, menadione and α-tocopherol). The rats were starved overnight before killing and were given tritiated thymidine (i.p.) before death. The object was to examine the influence of diet on the toxicity of single or repeated doses of AFB<sub>1</sub>. The deficient diet protected rats against a 7-9 mg/kg dose of AFB<sub>1</sub>. This dose was lethal to 60-100% of those rats given the adequate diet; 20% of the unaffected rats showed areas of abnormal hepatocytes, probably preneoplastic in composition. These results were only obtained in rats receiving one dose of AFB<sub>1</sub> since it was discovered that rats on the deficient diet were highly sensitive to repeated doses of AFB<sub>1</sub>.



In all cases, none of the protective compounds tested had any discernible effect. In fact, enhancement of AFB<sub>1</sub> toxicity by MEA was observed. Necrosis was found to varying degrees when histological studies were done on affected livers. Proliferation of bile duct cells was common, as was an increase in the size of periportal hepatocytes and focal hyperplasia. Resting levels of drug-metabolizing enzymes were low in livers of deficient rats and did not change in response to AFB<sub>1</sub> as did the same enzymes in rats fed the adequate diet. This suggests that metabolic products of AFB<sub>1</sub> are involved in both its toxicity and its carcinogenicity.

- 1559 *IN VIVO* INCORPORATION OF (1-<sup>14</sup>C) LEUCINE INTO RAT LIVER AND SERUM PROTEIN AFTER DIETARY SUPPLEMENTATION WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, CHLORAMPHENICOL OR BOTH COMPOUNDS. (E.) Blunck, J. M. (Dept. Path., U. Melbourne, Australia) and N. P. Madsen. *Chem-Biol Interact* 4(2):103-112, 1971/1972.

The effects of dietary 3'-methyl-4-dimethylaminoazobenzene (3'MeDAB) (0.06%), chloramphenicol (CAP) (2%), or both, on the *in vivo* incorporation of i.p.-injected <sup>14</sup>C-leucine into liver and serum protein was studied in male Sprague-Dawley rats. The specific activity of both liver and serum protein was significantly decreased in all treated groups; the decrease was more marked at 20 min than at 60 or 120 min, after injection of the <sup>14</sup>C and it was consistently greater in the CAP-fed than in the 3'MeDAB-fed group. When <sup>14</sup>C-leucine incorporation was standardized to liver mass, however, no difference in rate of incorporation was seen between experimental and control groups. An increase in protein content relative to liver mass accounted for the apparently decreased <sup>14</sup>C-leucine incorporation in the experimental groups. However, a positive correlation ( $r = 0.98$ ) was found between the specific activity of liver protein and total uptake of <sup>14</sup>C-leucine/g wet liver in control and experimental groups. This suggested that the relative availability of <sup>14</sup>C-leucine might have some bearing on the decreases in specific activity of the liver and serum proteins in the treated groups. Precursor pool analysis showed no consistent isotope dilution in the treated rats. 3'MeDAB or CAP had no effect on isotope distribution in liver lobules as determined autoradiographically. It is concluded that one effect of the dietary supplements is to alter the total uptake of the isotope into liver tissue. A similar relationship between the total uptake/g wet liver and the specific activity of the protein in the liver exists in all groups. Results of *in vitro* incorporation experiments are given in a subsequent report.

- 1560 DNA SYNTHESIS IN RAT LIVER DURING EARLY STAGES OF AZO DYE-INDUCED HEPATOCARCINOGENESIS. (E.) Rabes, H. M. (Inst. Path., U. Munich, Germany), R. Hartenstein and W. Ringelmann. *Cancer Res* 32(1):83-89, 1972.

DNA synthesis in different liver cell types of male Sprague-Dawley rats fed a daily diet containing 0.05% 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) was studied by autoradiography two hr after an i.p. injection of <sup>3</sup>H-thymidine. The L.I. (number of labeled cells per total number of pertinent cell type) and the relative number of each cell type, including parenchymal cells, and bile duct cells (including "oval" cells which had a round or oval nucleus and a small, strongly basophilic cytoplasm and which were seen in sinusoids starting 14 days after the start of dye feeding), were determined. The autoradiographic results were compared to a biochemical study done earlier by Sneider et al. on the same hepatic cell types. In agreement with biochemical results, the numerical proportions of different liver cell types were altered by 3'-MeDAB feeding. A minimum percentage of hepatocytes (40% of total cells) was seen at day 17 with a relative maximum of nonhepatic cells due primarily to an increase in bile duct cells (up from 3% on day 7 to 30% on day 17). DNA synthesis of bile duct cells began to increase ten days after the start of 3'MeDAB feeding and reached a maximum L.I. on day 14. Hepatocytes and mesenchymal cells started DNA synthesis after a similar lag period and showed a maximum L.I. on day 17. Hemopoietic cells showing a high L.I. were seen beginning on day 14 until the end of the experiment on day 42. The course of labeling of the different cell types determined by autoradiography in this study was similar to the pattern of <sup>3</sup>H-thymidine incorporation into the different nuclear fractions as determined by Sneider et al. In one set of autoradiographic experiments, animals were sacrificed at extended periods after <sup>3</sup>H-thymidine injection. In these cases, the L.I. of all cell types dropped. That of hemopoietic and bile duct cells decreased most rapidly while the L.I. of hepatocytes and mesenchymal cells showed less of a reduction. It is concluded that proliferation dynamics of various subpopulations of nonhepatic cells during early stages of liver carcinogenesis are highly heterogeneous and require a detailed morphological and autoradiographic analysis in addition to biochemical investigation.

- 1561 EARLY STAGE IN THE METABOLISM OF AMINOAZO DYES IN THE LIVER OF RATS. (E.) Du Plooy, M. (South African Counc. Sci. Indust. Res., Pretoria) and J. Dijkstra. *Chem-Biol Interact* 4(3):163-173, 1972.

*N,N*-Dimethylaminoazobenzene (DAB) was found to give rise to "early metabolites" in rat liver; these metabolites were trichloroacetic acid (TCA)-soluble and could not be extracted from TCA solution by ethyl ether. Fasting male albino rats were given 25 mg DAB by gastric intubation. After sacrifice livers were prepared for thin layer chromatography (TLC) analysis. TCA-soluble early metabolites were detectable within one hr after DAB administration; the maximum concentration of metabolites in liver was found four hr after dosing. The crude mixture of metabolites obtained by TLC from an ethanol extract of the DAB-dosed liver was fractionated by high-voltage paper electrophoresis into a group of dyes having six components; the two main fractions of this group of dyes

were identified as the ethereal-sulfates of 4'-OH-DAB and 4'-OH-monomethylaminoazobenzene.

- 1562 STUDIES ON PYRUVATE KINASE ISOZYMES IN RAT LIVER DURING AZO DYE CARCINOGENESIS. (Jap.) Torisu, T. (Cancer Res. Inst., Fukuoka, Japan). *Acta Med* 39(5):1-13, 1969.

A study of the effect on a carcinogen, 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) on the early stage of rat hepatocarcinogenesis is reported. A diet containing 0.06% 3'-Me-DAB was given to test animals for periods of 7, 15, 30, 45, 60, 90 and 120 days; the standard diet was then given for a recovery period of 60 days. Up to 60 days of the dye treatment, the livers showed no recognizable differences from normal livers in the histological preparations, in the mitotic rate, or in DNA and protein contents. Rabbit anti-muscle-type pyruvate kinase was produced, and antigenic differences between the muscle-type pyruvate kinase (M-PK) and the liver type pyruvate kinase (L-PK) were demonstrated. It was known that there was no elevation of total pyruvate kinase activity during the experiment. Using the anti-serum neutralization method, a pattern shift of the isozyme due to the dye administration was shown. A pattern shift from L-PK to M-PK was seen as early as 15 days after initiation of 3'-Me-DAB treatment, and the pattern persisted for at least 150 days. Partial hepatectomy (two-thirds), starvation (48 hours), alloxan (6 mg/100 g body weight), (insulin (3 x 15 units/100 g body weight) used to treat alloxan diabetics) and hydrocortisone acetate (5 x 25 mg/rat) produced no effect on the high level of M-PK in livers of rats that received 3'-Me-DAB for 60 days. That the partially hepatectomized animals maintained the same M-PK level during the regeneration for at least 20 days may suggest that the isozyme shift is heritable. A high M-PK level was thought to be a biochemical property of the precancerous state of the rat liver.

- 1563 INFLUENCE OF INSULIN ADMINISTRATION ON GROWTH OF THE 7,12-DIMETHYLBENZ(a)ANTHRA-CENE-INDUCED MAMMARY CARCINOMA IN INTACT, OOPHORECTOMIZED, AND HYPOPHYSECTOMIZED RATS. (E.) Heuson, J.-C. (Bordet Inst., Free U. Brussels, Belgium), N. Legros and R. Heimann. *Cancer Res* 32(2):233-238, 1972.

Mammary carcinomas were induced in random-bred, female Sprague-Dawley rats at age 50 days, by a single feeding of 20 mg of 7,12-dimethylbenz(a)anthracene (DMBA) dissolved in sesame oil. Fifteen weeks later, 68 tumor-bearing rats were randomly divided into four groups of 17 rats each. Group A, the control, received no treatment. Group B received 10% glucose (G) solution as drinking fluid. Group C was treated with insulin (2.5 i.u./100 g body wt s.c. daily, six days/week). Group D received both insulin and 10% G. The experiment lasted six weeks after which all rats were killed and autopsied and mean tumor size was determined by caliper measurement. Only histologically diagnosed carcinomas were con-

sidered. Tumor growth in rats given insulin and G (group D) showed an 8.3 fold increase in size compared to controls. Groups B and C showed increases of 2.2 and 4.8-fold resp., as compared to controls. In oophorectomized rats, administration of the same dose of insulin, together with the 10% G solution for four weeks, failed to prevent tumor regression resulting from oophorectomy. On the other hand, in hypophysectomized rats, administration of insulin for three weeks at a daily dose of 0.4 to 0.8 i.u./100 g body weight significantly reactivated tumor growth, as compared with a matched control group, when started 21 days after hypophysectomy. Both insulin-treated and control groups also received 10% G and daily s.c. injections of 1.5 mg ovine prolactin; the latter did not measurably reactivate tumor growth. It is concluded that insulin administered *in vivo* appears to display intrinsic growth-stimulating properties on mammary tumor tissue and that rat mammary carcinoma, in addition to being estrogen and prolactin dependent, is also insulin dependent.

- 1564 THE BINDING OF 7,12-DIMETHYLBENZ(a)ANTHRA-CENE TO MAMMARY PARENCHYMA DNA AND PROTEIN *IN VIVO*. (E.) Janss, D. (VA Hosp., Memphis, Tenn.), R. C. Moon and C. C. Irving. *Cancer Res* 32(2):254-258, 1972.

Fifty-day-old female Sprague-Dawley rats were sacrificed at various times 16 hr and 3, 7, 14 and 42 days following administration by gastric intubation of 20 mg <sup>3</sup>H-labeled 7,12-dimethylbenz(a)anthracene (DMBA), a potent skin carcinogen. The abdominal-in-guinal mammary glands were removed, and the parenchymal cells were separated. Parenchymal cell DNA and protein were isolated from cell homogenates and the DNA was purified by ultracentrifugation. DMBA binding to DNA was 47 pmoles/mg DNA at 16 hr after carcinogen administration. The level of DNA-bound DMBA remained relatively constant between 3 and 14 days, with 50% of the DNA-bound DMBA-<sup>3</sup>H at 16 hr still remaining after 14 days. By 42 days, bound DMBA had decreased to 14 pmoles/mg DNA. Only 22 pmoles/mg DMBA were bound to each milligram of protein at 16 hr postfeeding. The DMBA-protein complex remained at a constant level from days 3-7 and thereafter declined to 2 pmoles/mg protein at days 14 and 42. DNA content of mammary gland and parenchymal cells as determined by colorimetry gradually increased over the 42-day period, but the difference between the DNA content of DMBA-treated and control rats was not significant.

- 1565 METABOLISM AND MACROMOLECULAR BINDING OF DIBENZ(a,c)ANTHRACENE AND DIBENZ(a,h)ANTHRACENE BY EMBRYO CELLS IN CULTURE. (E.) Duncan, M. E. (Chester Beatty Res. Inst., London, England) and P. Brookes. *Int J Cancer* 9(2):349-352, 1972.

The metabolism and consequent macromolecular binding of the non-carcinogenic polycyclic hydrocarbon <sup>3</sup>H-dibenz(a,c)anthracene (DB(a,c)A) and the carcinogenic polycyclic hydrocarbon <sup>3</sup>H-dibenz(a,h)anthracene



(DB( $\alpha$ , $\hbar$ )A) were studied in mouse embryo cells. Cells were treated with  $^3\text{H}$ -DB( $\alpha$ , $\epsilon$ )A at either 0.94  $\mu\text{M}$  for 145 hr or 0.79  $\mu\text{M}$  for 72 hr and DB( $\alpha$ , $\hbar$ )A at either 0.92  $\mu\text{M}$  for 145 hr or at 0.51  $\mu\text{M}$  for 96 hr. The hydrocarbons were extracted from the medium with the chloroform-methanol method. The extent of metabolism was determined by measuring the radioactivity appearing in an upper phase of water added to the original chloroform-methanol extract. Metabolism of DB( $\alpha$ , $\hbar$ )A was considerably slower than that of DB( $\alpha$ , $\epsilon$ )A with only 27% of the radioactivity appearing in the water phase in the 145-hr sample compared to 87% for DB( $\alpha$ , $\epsilon$ )A. Both metabolism rates were slower than those found previously with other hydrocarbons. The binding index (extent of reaction of the hydrocarbon with the particular macromolecule resulting from metabolism of 1  $\mu\text{M}$  mole of hydrocarbon per milliliter of medium to which the cells were exposed) to DNA, RNA, and protein was low for the non-carcinogenic DB( $\alpha$ , $\epsilon$ )A (0.9 and 1.3, 1.8 and 2.3, and 8.3 and 9.3, resp.) and at least ten-fold higher for the carcinogenic DB( $\alpha$ , $\hbar$ )A (14 and 21, 18 and 35, and 17 and 36, resp.).

1566 SUPPRESSION OF 7,12-DIMETHYLBENZ( $\alpha$ )ANTHRACENE-PRODUCED ADRENAL NECROSIS BY STEROIDS CAPABLE OF INDUCING ARYL HYDROCARBON HYDROXYLASE. (E.)

Somogyi, A. (Hoffmann-La Roche Inc., Nutley, N. J.), K. Kovacs, B. Solymoss, R. Kuntzman and A. H. Conney. *Life Sci* 10(22):1261-1271, 1971.

Results of a study with adult female Sprague-Dawley rats pretreated p.o. with spironolactone, ethylestrenol, steroid SC 11927, pregnenolone-16 $\alpha$ -carbonitrile or dexamethasone acetate, for several days and challenged with i.v. injection of 7,12-dimethylbenz[ $\alpha$ ]anthracene (DMBA) are presented. Pretreatment with any of the above-mentioned compounds prevented adrenal necrosis when challenged with DMBA. Betamethasone offered only partial protection against DMBA. All the steroids but ethylestrenol produced an increase in hepatic metabolism of DMBA and benzo[ $a$ ]pyrene (BP). The study revealed a marked increase in DMBA and BP metabolism in the livers of the steroid-treated rats, with the exception of ethylestrenol, compared to rats treated with phenobarbital. These steroids may decrease the concentration in the target cells of toxic polycyclic hydrocarbons by inducing production of aryl hydrocarbon hydroxylase, thus stimulating the metabolism of DMBA and/or its metabolites.

1567 MYELOPEROXIDASE AND CRYSTALLINE BODIES IN THE GRANULES OF DMBA-INDUCED RAT CHLOROMA CELLS: ULTRASTRUCTURE, CYTOCHEMISTRY AND TISSUE CULTURE. (E.) Ioachim, H. L. (Coll. Physic. Surg., Columbia U., New York, N.Y.), S. Keller, M. Sabbath, B. Andersson, B. Dorsett and E. Essner. *Amer J Path* 66(1):147-162, 1972.

Chloroma, a rare type of myeloid leukemia, was induced by repeatedly administering 7,12-dimethylbenz[ $\alpha$ ]anthracene (DMBA) i.p. to a splenectomized Long-Evans rat. Once the cancer was established, tumor

fragments were removed and subjected to tissue culture techniques, to electron and light microscopy, and to various biochemical tests. It was found that chloroma affected the kidneys, liver, spleen, and lungs. Such diseased tissue was characterized by giant immature nuclei, containing distortions and bizarre processes; the chromatin was condensed and large nucleoli were present. Mitochondria were large, swollen, and often vacuolated. But the most consistent feature was the presence of granules of types A and B which were often associated with crystalline bodies. Other discoveries included the spontaneous red fluorescence of tumor cells when exposed to fluorescent light, and the presence of heme-containing porphyrins as indicated by spectrophotometry. Chloroma cells established in tissue culture retained the ability to induce chloroma tumors, but lost the capacity to produce myeloperoxidase, the peroxidative enzyme that imparts a green coloration to affected cells.

1568 TOXIC ACTIVITY AND METABOLISM OF CARCINOGENIC HYDROCARBONS IN NORMAL AND TUMOR CELL CULTURES FROM GOLDEN HAMSTER. (Rus.) Zavadina, S. P. (Acad. Med. Sci., Lab. Carcinogenesis Mechanisms, U.S.S.R.) and A. Ya. Khesina. *Vop Onkol* 17(7):62-66, 1971.

Toxic activity and metabolism of 3,4-benzo[ $a$ ]pyrene and 7,12-dimethylbenz[ $\alpha$ ]anthracene were studied on normal and virus-transformed embryo cell cultures from golden hamsters. The respective concentrations of the above hydrocarbons in the culture media were 1.0 and 0.1  $\mu\text{g}/\text{ml}$ . Both were metabolized to a greater degree by normal than by SV40- or polyoma virus-transformed cells. Normal cells proved to be more sensitive to the toxic effect of these hydrocarbons. 7,12-Dimethylbenz[ $\alpha$ ]anthracene had a cytostatic effect on transformed fibroblastic cells and a cytotoxic effect on normal cells. The metabolic rate was higher in tumor cells than in normal cells for both substances, with a lower value for 7,12-dimethylbenz[ $\alpha$ ]anthracene. The metabolism was more active in cells of high sensitivity. However, it was not always possible to find a correlation between cell sensitivities and metabolic rates. The differences in sensitivities of diverse cultures to the above substances may be explained by the differences in the rates of metabolism and in the nature of the metabolites.

1569 EFFECT OF 7-HYDROXYMETHYL-12-METHYLBENZ( $\alpha$ )-ANTHRACENE ON THE ADRENAL GLAND OF THE FOETAL AND POSTNATAL RAT. (E.) Bird, C. C. (U. Med. Bldgs., Aberdeen Scotland) and A. M. Crawford. *J Path* 104(3):191-199 (and Plates LXXII-LXXIV), 1971.

The hydrocarbon 7-hydroxymethyl-12-methylbenz[ $\alpha$ ]anthracene (7-OHM-12-MBA) has been shown to have a powerful adrenocorticolytic action in the mature rat. This study focuses on the effect of 7-OHM-12-MBA on the adrenal gland of the rat fetus and the immature postnatal rat. In the initial part of the study, pregnant

Sprague-Dawley female rats received at various times a single injection of 7-OHM-12-MBA dissolved in olive oil; control females received only olive oil. The uptake of tritiated thymidine by adrenal glands of fetuses of rats given 7-OHM-12-MBA was also observed. It was found that those treatments given on days two through 11 caused no histologic damage to the fetal adrenal gland. On day 12 treatment produced a slight reduction of glandular weight, while on days 13 through 16 7-OHM-12-MBA injections caused severe size reduction of the adrenal gland so that it either was impossible to dissect it free of the adjacent tissue or was not macroscopically identifiable at all. On days 17 through 21 injections of the hydrocarbon produced severe necrosis, often affecting subsequent healthy arrival. Maternal adrenal glands showed corresponding damage. Tritiated thymidine uptake of the treated fetuses was first reduced, followed by a period of increased uptake, and then leveled off to normal. This can be attributed, at least in part, to a temporary reduction in DNA synthesis by the adrenocortical cells. Again, the maternal response was similar to that of the fetuses'. In the second part of the experiment, postnatal rats were subjected to a single 7-OHM-12-MBA injection i. p. It was found that female rats over 30-days-old were more susceptible to the hydrocarbon than the males of the same age. However, both sexes were resistant at ages younger than 30 days. Controls throughout the experiments developed normal adrenal glands.

- 1570 METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN NORMAL AND 3-METHYLCHOLANTHRENE (MC)-TREATED MICE: DISTRIBUTION OF THE PRINCIPAL METABOLITES IN THE DIGESTIVE TRACT AND THE MESENTERY. (Fr.) Gentil, A. (Inst. Sci. Res. Cancer, Val-de-Marne, France), C. Lasne and I. Chouroulinkov. *C R Acad Sci (Paris)* 273(19):1763-1766, 1971.

The distribution of the principal metabolites of tritiated 7,12-dimethylbenz(a)anthracene carrying 30  $\mu$ C radioactivity (7-hydroxymethyl-12-methylbenz(a)anthracene, 12-hydroxymethyl-7-methylbenz(a)anthracene and 8,9-dihydro-8,9-dihydroxy-7,12-dimethylbenz(a)anthracene) in the digestive tract of normal mice and those pretreated 40 hours earlier with a 2 mg dose of methylcholanthrene was studied. The metabolites were determined in different organs two, four, eight and 15 hours after the 7,12-dimethylbenz(a)anthracene was administered by means of a gastric tube. Varying quantities of metabolites were detected in all organs except for the mesentery. The highest and fairly stable quantities were revealed in the liver (64 and 55 in normal mice after two and 15 hours, and 44 and 63 in stimulated mice after two and 15 hours expressed in % of total radioactivity). The metabolites' concentrations in the small intestine showed a rapid drop from 29 after two hours to 13 after four hours in normal mice. As opposed to 8,9-dihydro-8,9-dihydroxy-7,12-dimethylbenz(a)anthracene, hydroxymethyl derivatives were formed in higher amounts in both stomach and small intestine than in liver; these hydroxymethyl products may be intermediary metabo-

lites that are, finally, decomposed by the liver. The production of dihydrodiol was only affected by methylcholanthrene, causing slight increase in dihydrodiol in the small intestine and the liver. As the metabolite concentrations showed no increase with time, the metabolites may have been formed primarily *in situ* in the investigated tissues. The DMBA may have been partly metabolized by the digestive mucosa before being distributed in the organism, which suggests a possible antitoxic function of the digestive tract. The absence of metabolites in the mesentery may indicate that DMBA acts on this level in its primary form.

- 1571 EFFECT OF SPIRONOLACTONE AND PROADIFEN ON 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED HAEMATOLOGIC CHANGES. (E.) Solymoss, B. (U. Montreal, Canada), A. Somogyi and K. Kovacs. *Haematologia* 5(1-2):87-96, 1971.

Female Sprague-Dawley rats were fed 7,12-dimethylbenz(a)anthracene (DMBA) to induce bone marrow lesions with concomitant hematopoietic failure. Some of the carcinogen-treated rats were given spironolactone, a pharmaceutical agent, to suppress hematologic changes. In rats given DMBA only, bone marrow damage was initiated as early as 24 hours after DMBA administration, while peripheral blood reactions took six days to commence. In the peripheral blood of DMBA-treated animals, the following changes were observed: slight thrombocytopenia, decreased total leucocyte count, diminution of polymorphonuclear neutrophils and lymphocytes, and decreased numbers of monocytes. Lesions in bone marrow of DMBA-treated animals were characterized by: dilatation of the capillaries, congestion, aggregation of erythrocytes, hemorrhages and intravascular accumulation and margination of polynuclear leucocytes. Blood of animals given DMBA plus spironolactone showed diminished DMBA-induced alterations in the leucocyte counts; these animals showed more rapid and intense regeneration of injured bone marrow. Twelve days after DMBA, marked anemia, severe thrombocytopenia and complete absence of polychromatophilic erythrocytes in blood were observed. None of these changes was prevented by spironolactone. In further studies, both DMBA and spironolactone were given via injections; another chemical suppressant, proadifen, was administered in some cases. The DMBA acted in a manner similar to that in the preceding tests; however, spironolactone and proadifen prevented all changes in bone marrow and blood.

- 1572 MUTAGENIC ACTION, LOSS OF TRANSFORMING ACTIVITY, AND INHIBITION OF DEOXYRIBONUCLEIC ACID TEMPLATE ACTIVITY IN VITRO CAUSED BY CHEMICAL LINKAGE OF CARCINOGENIC POLYCYCLIC HYDROCARBONS TO DEOXYRIBONUCLEIC ACID. (E.) Maher, V. M. (Marygrove Coll., Detroit, Mich.), S. A. Lesko, Jr., P. A. Straat and P. O. P. Ts'o. *J Bact* 108(1):202-212, 1971.

Repeated stepwise iodine-induced chemical reactions of tritiated 3,4-benzopyrene (3,4-BP) or tritiated



dimethylbenzanthracene (DMBA) with transforming DNA of *Bacillus subtilis* SB 19 resulted in the covalent binding of as many as one hydrocarbon molecule per 60 to 100 DNA nucleotides. The presence of such chemically bound hydrocarbons on the DNA caused a loss of the ability of the DNA to transform recipient T3 strains of cells, but increased the frequency of forward mutations when transformations did occur. In addition, the mutations reverted at a rate of 33% or less in all of the cases studied. The presence of the hydrocarbons also caused cross-linking of DNA strands, thus interfering with the transcription of the molecule by RNA polymerase. All of the hydrocarbon-DNA samples showed much lower levels of survival of biologic activity when assayed in recipient strains which are known to be deficient in the enzymes required for repair of ultraviolet light-induced damage to DNA. 3,4-BP linked covalently to calf thymus DNA at a level of approximately one hydrocarbon molecule per 330 bases was shown to cause up to 80% inhibition of the *in vitro* transcription of the DNA by highly purified ribonucleic acid polymerase prepared from *Micrococcus luteus* under the experimental condition of template saturation. The presence of 3,4-BP and DMBA molecules covalently bound to *B. subtilis* DNA samples was also found to prevent complete denaturation of the bihelical structure of certain DNA molecules and thus appears to effect a cross-link in these DNA molecules.

- 1573 INCIDENCE OF BENZOPYRENE-INDUCED TUMORS IN LINES OF MICE GENETICALLY SELECTED FOR "HIGH" AND "LOW" ANTIBODY PRODUCTION. (E.) Biozzi, G. (Broussais Hosp., Paris, France), C. Stiffel, D. Mouton, Y. Bouthillier and C. Decreusefond. *Transplantation Proc* 3(3):1333-1336, 1971.

Random-bred Swiss mice were genetically selected for "amount of antibody" produced after immunization with optimal doses of heterologous erythrocytes. The mice were progressively separated into "high" and "low" responding lines during selective breeding until a maximal interline separation was reached after 20 generations. The two lines were first tested by spleen inoculation for humoral antibody responsiveness to histocompatibility antigens. It was found that the "high" line produced a high titer of cytotoxic antibodies to "low" line spleen cells, while the "low" line produced a low titer in response to "high" line spleen cells; however, interline skin graft studies showed rejection in both strains at the same time. Genetic selection operated only on humoral responsiveness, while cell-mediated immunity was not affected. Finally, mice of the sixteenth and nineteenth generations of both the "high" and the "low" lines were injected with benzopyrene. Tumors developed much more readily and grew more rapidly in the "low" line, showing that resistance to tumor formation is probably related to humoral immune responsiveness.

- 1574 RESPIRATORY TRACT TUMORS IN HAMSTERS AFTER INTRATRACHEAL INSTILLATIONS OF BENZO(a)PYRENE ALONE AND WITH FURFURAL. (E.) Feron, V. J.

(Central Inst. Nutrition Food Res., Zeist, Netherlands). *Cancer Res* 32(1):28-36, 1972.

Three groups of ten wk. old randomly bred Syrian golden hamsters, each consisting of 35 males and 35 females, received 36 weekly intratracheal instillations of 0.2 ml furfural (1.5% in 0.9% saline), 0.2 ml benzo(a)pyrene (BP) (0.5% carrier-free suspension in 0.9% saline), or BP plus furfural, resp. A control group of 35 males received 0.9% saline solution. The experiment was terminated after 78 wk. when nearly all animals treated with BP or BP plus furfural had died or been sacrificed. Average weights of males treated with BP plus furfural were lower than those of males in other groups and were significantly lower than those of control after wk. 16. The BP plus furfural group had the lowest survival rate, presumably due to a high incidence of peritracheal sarcomas (20 out of 61) not seen in the other groups. BP alone induced respiratory tumors in 41 of 62 hamsters examined, with squamous cell carcinoma being the most frequent tumor observed (33 of 62). Treatment with BP plus furfural, when compared to treatment with BP alone, resulted in earlier development of metaplastic changes of the tracheobronchial epithelium and a shorter latent period for the development of tracheobronchial tumors. Peripheral (lung) adenomatoid lesions appeared as proliferations of bronchioalveolar epithelium which spread along the alveoli and were found most commonly (47 of 62) in animals given BP alone. No metastases of any of the respiratory tract tumors were observed. Only four tumors were found at sites other than the respiratory tract and these were considered spontaneous. There was no indication that hepatic (multiple cysts, parenchymal destruction, pericystic hemorrhages and fibrosis) and renal (amyloidosis) changes were related to treatment. The results of the study provide no evidence for tumorigenic activity in the respiratory tract by furfural. Furfural did, however, appear to have an augmenting effect on the induction of peritracheal sarcomas by BP. It was concluded that neither a carrier substance nor a surface active agent is required for the induction of respiratory tract tumors by BP particles administered intratracheally.

- 1575 CARCINOGENIC HYDROCARBONS AND HUMAN CELLS IN CULTURE. (E.) Brookes, P. (Chester Beatty Res. Inst., London, England) and M. E. Duncan. *Nature* 234(5323):40-43, 1971.

Experiments designed to compare the effects of carcinogenic hydrocarbons on primary human embryo cells and on human tumor cells (HeLa) are described. The metabolism and binding of <sup>3</sup>H-labeled benzo(a)pyrene (B(a)P) and 7,12-dimethylbenz(a)anthracene (DMBA) were tested in HeLa cells and in human embryo fibroblast cultures (including lung, skin/muscle and gut). The results were compared with values found previously for mouse embryo cells. The results showed: 1) in human embryo cells, the rate of hydrocarbon metabolism (B(a)P) is similar to that found in rodent embryo cells, as in B(a)P binding to macromolecules; 2) the DMBA binding index in the human cells is markedly less than the value obtain-

ed for mouse embryo cells; 3) in HeLa cells the DMBA metabolism is slower; 4) the binding of B(a)P to RNA, DNA and protein is much less in HeLa cells than in primary human lung cells; and 5) DMBA binding is quite similar in both cell types. These studies indicate that the necessary conditions for transformation of human lung cells by B(a)P do exist.

- 1576 DOSE-RESPONSE STUDIES IN EXPERIMENTALLY INDUCED LUNG TUMOURS. (E.) Shabad, L. M. (Inst. Exp. Clin. Oncol., Moscow, U.S.S.R.). *Environmental Res* 4:305-315, 1971.

The results of some experimental investigations by the author and his colleagues during the past several years are presented. The development of lung adenomas in mice, their frequency, and their rate of growth has been shown to be dependent on the dose of the carcinogen. This has been demonstrated not only in adult animals but also under conditions of transplacental transmission and of organ cultivation of lung tissue. An experimental model of lung cancer in rats was created with the intratracheal administration of high doses of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) mixed with black India ink powder and suspended in Infusine, a "nonanaphylactogenic casein solution". Lung cancer was induced in approximately 70% of experimental animals with BP and in 30% with DMBA. The induced tumors were morphologically similar to human lung cancers. The "nonanaphylactogenic casein" and black India ink powder acted as adsorbents promoting the deposition and retention of the carcinogenic hydrocarbon in lung tissue. A systematic study of dose-response effects in the induction of experimental bronchogenic carcinomas and precancerous lesions revealed that the incidence rate of malignant tumors and precancerous lesions decreased with descending doses of the carcinogen. Repeated injections gave a greater carcinogenic effect than did a single instillation of the same dose. "Borderline" doses did not induce cancer but precancerous lesions were found. The existence of a dose-response effect can serve as a basis for cancer prevention.

- 1577 EFFECT OF IODINE ON THE CARCINOGENICITY OF 3,4-BENZOPYRENE. (E.) Nagata, C. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan), T. Tagashira, M. Inomata, and M. Kodama. *Gann* 62(4):309-314 (and plates LVIII-LX), 1971.

Female mice of ddN strain, about 30 days of age and weighing 18-20 g were given a single s.c. injection of benzo(a)pyrene (BP). Iodine, which is known to produce a cation radical of BP, was injected at the same site immediately afterwards. No accelerating effect on the carcinogenicity of BP was observed in experiments using tricaprylin and benzene as a solvent. BP in tricaprylin was more carcinogenic than in benzene. This solvent effect may result from the fact that benzene disperses instantaneously from the site of injection, whereas tricaprylin stays at the

site of injection maintaining the activity of BP. These results do not lend support to the proposition that the cation radical of BP is a proximate form of BP

- 1578 INDUCTION AND REPRESSION OF MICROSOMAL DRUG-METABOLIZING ENZYMES BY POLYCYCLIC HYDROCARBONS AND PHENOBARBITAL: THEORETICAL MODELS. (E.) Venkatesan, N. (U.S. Public Hlth. Serv. Hosp., New Orleans, La.), J. C. Arcos and M. F. Argus. *J Theor Biol* 33:517-537, 1971.

The polycyclic hydrocarbon 3-methylcholanthrene (MCA) and the drug phenobarbital were studied to determine their *in vivo* relation to oxidative enzymes in the liver. As inducing agents of aminoazo dye N-demethylase and other mixed function oxidases, these two compounds were found to increase the amount of enzyme protein available in the cell. When acting as repressors of dimethylnitrosamine (DMN) demethylase chemical action was mainly directed to regulation of the enzyme level. Such evidence indicates that MCA and phenobarbital stimulate the gene action system, possibly by pseudohormonal effects, and suggests that the synthesis regulation of microsomal mixed-function oxidases is highly specific and selective. The following models were thus postulated: 1) the Jacob-Monod operon model of the genetic regulatory mechanism of protein synthesis was used to explain how a substance (MCA or phenobarbital), the "inducer," combines allosterically with an "active repressor" leading to derepression in the case of "active enzymes," or combines allosterically to form a "corepressor" to activate otherwise inactive repressors in the case of "repressible" enzymes; 2) the Jacob-Monod model was extended to include "cascade control" through which different sets of genes coding for inducible and repressible microsomal oxidative enzymes are turned on or off by a chemical substance; 3) translational control of gene expression by which a substance prohibits the relative movement of messenger RNA and the ribosome to block completion of the polypeptide chain may also be involved.

- 1579 EFFECTS OF 3-METHYLCHOLANTHRENE ADMINISTRATION ON THE PROTEINS OF ENDOPLASMIC RETICULUM. (E.) Black, O., Jr. (Baylor Coll. Med., Houston, Tex.), E. T. Cantrell, R. J. Buccino and E. Bresnick. *Biochem Pharmacol* 20(12):2989-2998, 1971.

The *in vivo* effects of 3-methylcholanthrene (3-MC) on the incorporation of  $^{14}\text{C}$ -amino acid and  $^3\text{H}$ -aminolevulinic acid into proteins of smooth endoplasmic reticulum (SER) and rough endoplasmic reticulum (RER) of the rat liver are reported. Rats were given 3-MC and/or  $^{14}\text{C}$ -amino acid mixture and  $^3\text{H}$ -aminolevulinic acid in i.p. injections of 20 mg/kg, 1.45 mc/m-mole and 588 mc/m-mole, resp. Gel electrophoretograms of solubilized liver proteins of SER and RER of controls (i.e., rats given  $^{14}\text{C}$ -amino acid or  $^3\text{H}$ -aminolevulinic acid but no 3-MC) and 3-MC-treated rats were made. 3-MC appeared to cause a more rapid incorporation of amino acids into SER and RER and a slower degradation of the proteins



of these fractions. 3-MC pretreatment left the relative amount of protein in the SER unaltered; RER however, was slightly elevated 22 hr after pretreatment with 3-MC. After an incorporation period of seven min, the specific activity of  $^{14}\text{C}$ -amino acid in RER was slightly higher than in SER, in both control and 3-MC-treated rats. The same major protein species incorporated  $^3\text{H}$ -aminolevulinic acid, a heme precursor, and the  $^{14}\text{C}$ -amino acids. Pretreatment of rats with 3-amino-1,2,4-triazole, an inhibitor of heme synthesis, resulted in a reduction in the amount of both the  $^{14}\text{C}$ -amino acid and the  $^3\text{H}$ -aminolevulinic acid incorporation. It was thought that a substantial portion of microsomal protein is hemoprotein.

- 1580 EFFECTS OF 3-METHYLCHOLANTHRENE AND SOME RELATED COMPOUNDS UPON THE BENZOPYRENE HYDROXYLASE ACTIVITY IN FETAL RAT LIVER EXPLANTS. (E.) Burki, K. (Baylor Coll. Med., Houston, Tex.), R. A. Seibert and E. Bresnick. *Biochem Pharmacol* 20:2947-2952, 1971.

Sprague-Dawley rat fetuses were subjected to liver explantation procedures, and the livers were established in organ cultures. At varying times after liver explantation, cultures of liver tissue were treated with the polycyclic hydrocarbon 3-methylcholanthrene (3-MC) or with one of four 3-MC derivatives: 1-keto-3-MC; 1-hydroxy-3-MC; cis-11,12-dihydroxy-11,12-dihydro-3-MC; and trans-1,2-dihydroxy-3-MC. The activity of the microsomal mixed-function oxygenase, benzo(a)pyrene (BP) hydroxylase, in treated cultures was then determined by fluorescence studies. It was found that addition of the above compounds effected a marked increase in the activity of BP hydroxylase. Addition of 3-MC and 1-keto-3-MC caused a four-fold elevation in BP hydroxylase, while the 1-hydroxy- and the cis-11,12-dihydroxy-11,12-dihydro-3-MC derivatives produced stimulatory activities of only 2.7- and two-fold, resp. Trans-1,2-dihydroxy-3-MC was the most potent agent, causing a 6.7-fold increase in enzyme activity. When 3-MC or its derivatives was added to fresh fetal liver explants, a lag of 6-12 hours was seen between treatment and increased BP hydroxylase activity; when the agents were added to 40-hour pre-incubated explant cultures, however, there was a more immediate increase in enzyme activity.

- 1581 ACTIVATION AND ISOLATION OF HAMSTER-SPECIFIC C-TYPE RNA VIRUSES FROM TUMORS INDUCED BY CELL CULTURES TRANSFORMED BY CHEMICAL CARCINOGENS. (E.) Freeman, A. E. (Microbiol. Associates, Inc., Bethesda, Md.) G. J. Kelloff, R. V. Gilden, W. T. Lane, A. P. Swain, and R. J. Huebner. *Proc Nat Acad Sci USA* 68(10):2386-2390, 1971.

Syrian hamster cell cultures, derived from embryos of the strains LSH and NIH, were subjected to two carcinogenic chemicals, 3-methylcholanthrene and cigarette smoke condensate. Some of the cell lines transformed after such chemical exposure either remained viable or became necrotic. The transformed viable cultures were tested for complement fixation

against hamster-specific leukemia virus (HaLV) serum, but none of the cultures was clearly positive. Viable transformed cells were then injected into newborn hamsters to determine tumor-production possibilities. It was found that transformed cells produced malignant growths which could subsequently be cultured. Such malignant tumor cultures were tested by complement fixation and it was found that six of the nine lines contained significant quantities of HaLV group specific antigen. Tritiated uridine for uptake by viral RNA was added to the cultures for verification. The results showed the presence of virus. Virus particles were then isolated and disrupted by Tween 80-ether and HaLV antigen reactions were obtained. C-type virus particles were identified by electron microscopy and the isolates proved infectious to normal hamster cultures. However, all tumor cell lines were negative in gel diffusion tests as well as in complement fixation studies with antisera specific for murine leukemia virus. It is thus clear that this virus is of hamster origin and not merely a host-adapted murine leukemia virus, since the virus contained hamster specific antigen and because no mouse sarcoma viruses were used as activating agents. The authors favor the interpretation that HaLV exists in a repressed state in most, if not all, normal hamster cells. Activation may occur due to aging, irradiation, and/or chemical exposure, but is rare in all cases.

- 1582 MALIGNANT TRANSFORMATION OF MOUSE KIDNEY CELLS IN VITRO BY 20-METHYLCHOLANTHRENE. (E.) Nagata, T. (Dept. Anat., Shinshu U., Japan). *Med J Shinshu Univ* 15(3):131-151, 1970.

Primary mouse kidney cultures treated with 20-methylcholanthrene (MC) at concentrations of 5, 10 and 50  $\mu\text{g}/\text{ml}$  were observed to transform into permanent cell lines in two of five cases. All 15 untreated cultures died. The transformed lines had altered karyotypes, exhibited a random, multilayered distribution in culture and were epithelioid. One line had a large number of metacentric and submetacentric chromosomes whereas the other line had mostly telocentrics. Injection of more than  $10^5$  cells into newborn mice produced palpable carcinomas in 11 of 16 mice. These tumors regressed spontaneously in all mice given implants and not killed.

- 1583 A SEARCH FOR NITROSAMINES IN EAST AFRICAN SPIRIT SAMPLES FROM AREAS OF VARYING ESOPHAGEAL CANCER FREQUENCY. (E.) Collis, C. H. (Guy's Hosp. Med. Sch., London, England), P. J. Cook, J. K. Foreman and J. F. Palframan. *Gut* 12(12):1015-1018, 1971.

Following a report that nitrosamine-like substances had been found in home-made spirits distilled from a fermentation of maize husks and sugar in an area with a high incidence of esophageal tumors (Zambia), samples of alcoholic drinks were collected from a range of areas in East Africa (western Kenya and southern Uganda) where cancer of the esophagus occurs with

moderate to low frequency. Forty-four samples were given preliminary screening by polarography and those samples which showed reduction waves that might be due to nitrosamines (some samples as high as 21 ppm) were further analyzed by the more sensitive methods of gas chromatography and mass spectrometry. Samples from areas of similar tumor incidence were grouped and analyzed. Analysis by gas chromatography showed no evidence (<0.1 ppm or not detected) for the occurrence of methylethyl nitrosamine, diethyl nitrosamine, dipropylnitrosamine, ethylbutyl nitrosamine, dibutyl nitrosamine or N-nitrosopiperidine. Traces of compound having a similar retention time as dimethylnitrosamine (DMN) were observed (0.1-0.9 ppm). Subsequent examination by mass spectrometry showed no evidence of DMN. No nitrosamines were detected in a 2000 ml sample of spirit from a high tumor incidence area when the spirit sample was analyzed within ten days of manufacture. There was no apparent association between the levels of a DMN-like compound found in trace quantities and the frequency of cancer of the esophagus. The results of gas chromatography and mass spectrometry confirmed that polarography is too unspecific to be a useful indicator of nitrosamines.

- 1584 DIMETHYLNITROSAMINE: FORMATION OF MUTAGENIC COMPOUNDS BY INTERACTION WITH MOUSE LIVER MICROSOMES. (E.) Mallin, H. V. (Carcinogenesis Program, Oak Ridge Natl. Lab., Tenn.) *Mutat Res* 13(4):425-429, 1971.

A study of the mutagenicity of the metabolic breakdown products of dimethylnitrosamine (DMN) is reported. DMN (225  $\mu$ moles) was incubated with a suspension of mouse liver microsomes in the presence of an indicator organism for mutagenicity. The livers of four to six 10 to 14-week-old mice [B6C3F<sub>1</sub>/(C57BL/6 female x C3H male)] were used. Four different histidine-requiring strains of *Salmonella typhimurium* were used as indicator organisms (TA 1530, G46, C207 and C3076); the induction of mutations was scored by observing histidine revertants in any of the four strains. It was found that only those *S. typhimurium* strains which revert by base-pair substitution do so after treatment with DMN and liver enzymes. The number of reversions scored per 10<sup>6</sup> survivor *S. typhimurium* were 8.75, 30.1, 0.09 and 0.54, resp., for the four different strains. The kinetics of mutation induction in the TA1530 strain of *S. typhimurium* were exponential and the mutation frequency increased with (approximately) the 3.3 power of the treatment time. It was concluded that liver enzymes can form mutagenic compounds from DMN, and that these compounds are stable enough to enter the bacterial cell and induce mutations.

- 1585 ANALYSIS OF DNA FOR THE FORMATION OF 3-METHYLTHYMINE AFTER ADMINISTRATION OF DIMETHYLNITROSAMINE. (E.) Craddock, V. M. (Med. Res. Coun. Lab., Carshalton, Surrey England,). *Chem-Biol Interact* 4(3):149-154, 1972.

The nature of the <sup>14</sup>C-labelled component in the pyrimidine fraction of nucleic acids of cells from animals treated with <sup>14</sup>C-dimethylnitrosamine was studied to determine whether 3-methylthymine was formed in DNA after carcinogen treatment. Female Wistar albino rats of the Porton strain were given an i.p. injection of <sup>14</sup>C-dimethylnitrosamine (30 mg/kg) and sacrificed five or 24 hr later. DNA and RNA from treated rats were analyzed by column chromatography on Dowex-50 for free bases. In DNA analyses, the thymidine peak was labelled to an extent of 50 cpm/mg DNA. Seventy-seven percent of radioactivity cochromatographed with marker 3-methylthymine in an isopropanol-HCl-water solvent; however, an n-butanol-NH<sub>3</sub>-water solvent separated radioactivity from marker 3-methylthymine. This suggested that the labelled component of the DNA was not 3-methylthymine. The labelled component was not a product of methylation of the nucleic acid. Rather, it was hypothesized that the radioactive component might represent a compound labelled by the formaldehyde formed from dimethylnitrosamine. This component may be an uncharged metabolite of formaldehyde which becomes more extensively bound to DNA than to RNA.

- 1586 LABELING *IN VIVO* OF RAT LIVER PROTEINS BY TRITIUM-LABELED DIMETHYLNITROSAMINE. (E.) Mirvish, S. S. (Weizmann Inst. Sci., Rehovot Israel) and H. Sidransky. *Biochem Pharmacol* 20(12):3493-3499, 1971.

The effects of dimethylformamide (DMF), diethylformamide (DEF), 3-methylcholanthrene (3-MC), aminoacetone nitrile (AAN) bisulfate, and phenobarbitone sodium on the *in vivo* labeling of rat liver proteins by <sup>3</sup>H-dimethylnitrosamine (DMN) are reported. Rats were injected i.p. with 14.5 mg and 100  $\mu$ C <sup>3</sup>H-DMN; the test compounds were given by i.p. injection at various times before DMN. Phenobarbitone and 3-MC slightly inhibited protein labeling when given to adult rats as a pretreatment (15-19% inhibition). A greater (76-92%) inhibition of labeling was seen in rats pretreated with either DMF, DEF or AAN. When either ethionine or carbon tetrachloride was injected prior to DMN, protein labeling was inhibited. These inhibitory effects on the labeling of liver proteins correlated with known effects of the test compounds on the metabolism of DMN. These results suggested that DMN must be metabolized before it reacts with cell macromolecules.

- 1587 EFFECT OF A SINGLE DOSE OF DIMETHYLNITROSAMINE ON BIOSYNTHESIS OF NUCLEIC ACID AND PROTEIN IN RAT LIVER AND KIDNEY. (E.) Stewart, B. W. (Middlesex Hosp. Med. Sch., London, England) and P. N. Magee. *Biochem J* 125:943-952, 1971.

Female Wistar rats were fed a protein-deficient diet for one wk, after which the chemical carcinogen dimethylnitrosamine (DMN) was administered i.p. in a single dose. The rats were maintained on the defici-



ent diet for a further wk while various radioactive-biochemical tests were performed; rats were killed for histological study of liver tissue up to seven days after DMN administration. DMN caused a marked decrease in amino acid incorporation into liver protein. A transitory rise in incorporation two hr after injection was followed by a sharp decrease; the lowest point was reached nine hr after injection. Levels returned to normal in the liver at 19-48 hr, with a second marked decrease at three days. There were no changes, however, in hepatic DNA synthesis in the first 19 hr, but a tenfold increase was noted thereafter. In the kidney, DMN-induced changes began with an amino acid uptake doubling at two hr post-injection, followed by a leveling to the control value by 19 hr. A second peak was reached at three days, after which levels again returned to normal. Finally, a third peak was noted six days after treatment; a return to normal on the seventh day concluded the reaction. Other marked changes in the kidney cells were a failure of kidney cell nuclei to sediment through 2.3 M sucrose, decrease of DNA content and inhibition of RNA synthesis. These findings suggested that the nuclei are severely affected in the kidney at the time when the most marked kidney changes are seen, three days after DMN administration.

- 1588 ETHYLNITROSOUREA-INDUCED TRANSPLANTABLE TUMORS OF THE PERIPHERAL NERVOUS SYSTEM IN INBRED RATS. (E.) Wechsler, W. (Max-Planck-Inst. Hirnforschung) and M. A.-E. Ramadan. *Naturwissenschaften* 58(11):577, 1971.

Transplacental administration of ethylnitrosourea (ENU) in the BD IX strain of rats stimulated the growth of two primary tumors at the cervical and lumbar roots of the spinal cord. After 185 days the tumors were of medium size and presented histologic and ultrastructural characteristics of malignant neurinomas. Both tumors were later established as homo-transplants in the BD IX rats by s.c. inoculation of .05-plants in the BD IX rats by s.c. inoculation of .05-.5 g of tumor tissue. To date the tumors have been passed through 15 generations of rats over a period of 15 months. The transplanted tumors have retained many of the structural features of the primary tumor. Studies are being carried out to determine whether sarcomatous changes will occur with continued transplantation.

- 1589 THE INDUCTION OF TUMORS OF THE NERVOUS SYSTEM WITH INTRAVENOUS METHYLNITROSOUREA. (E.) Swenberg, J. A. (Dept. Veterin. Path., Ohio St. U., Columbus), A. Koestner and W. Wechsler. *Lab Invest* 26(1):74-85, 1972.

Repeated i.v. administration of methylnitrosourea (MNU) (5 mg per kg of MNU per week for 36 weeks) resulted in the production of neurogenic neoplasms in 97% of the experimental rats. Animal survival time and tumor incidence depended on the sex and strain of rat. Sprague-Dawley (CD) males had the shortest median survival time (265 days) followed by Fischer (CDF) males (285 days), CD females (336 days) and

CDF females (446 days). No extraneural tumors developed in males of either strain. Two of nine CD females and six of 11 CDF females developed a total of 12 extraneural neoplasms including mammary fibroadenomas, GU tract sarcomas, and "mononuclear cell" leukemias (only in CDF females). Male CD rats had the highest incidence of grossly detectable brain tumors (nine of nine). Multiple neuroectodermal neoplasms were present in the central nervous system of 17 of 35 rats with a total of three tumors in the spinal cord and 55 in the brain. Tumors showed a predilection for developing in periventricular regions of the lateral ventricles and subcortical white matter. Tumors were characterized by light and electron microscopy as astrocytomas, oligodendrogliomas, mixed gliomas, anaplastic gliomas or gliosarcomas. Twenty-one of 29 macrotumors were poorly differentiated and classified as anaplastic gliomas (14) or gliosarcomas (seven). Microtumors were well differentiated and were classified as oligodendrogliomas, mixed gliomas or as astrocytomas. A gradual transition from focal glial proliferation to macrotumors was observed. Astrocytomas were uncommon (five of 58 tumors) and occurred only as microtumors of the brain. Little necrosis and few mitoses were observed. Oligodendrogliomas were the most common microtumor (18 of 37 microtumors). Mixed gliomas were almost equally divided between micro- and macrotumors. They contained minimal necrosis, few mitoses and mild to moderate degrees of vascular proliferation. Anaplastic gliomas were the most common macrotumor (14 of 21 macrotumors). None was seen as a microtumor. Characteristic glial filaments and microtubules were seen in gliomas and gliomatous portions of gliosarcomas. Sarcomatous regions in gliosarcomas occasionally formed collagen. Neoplastic Schwann cells appeared to be the principal component of neurinomas, which were seen in the peripheral system, since a complete or partial basement membrane was associated with most tumor cells. More than half the neurinomas were found in CDF rats while less than one-fourth of CD rats developed them. None occurred in CD females.

- 1590 TUMOR INDUCING EFFECTS OF METHYLNITROSOUREA IN MICE. (Ger.) Eckert, H. (Humboldt U. Berlin, Germany) and E. Seidler. *Arch Geschwulstforsch* 38(1):7-9, 1971.

The organotropic action of methylnitrosourea (MNU), known specifically to induce tumors of the central nervous system in rats and rabbits, was studied in 60A and 20C3H mice. The animals were divided into four groups and given 5.0, 7.5, 10.0 and 15.0 mg/kg MNU, respectively, i.p. once weekly for ten months. The 7.5-mg/kg dose was administered to C3H mice; the other doses were given to A mice. At the end of the experimental period tumor incidence was 11/20, 3/20, 3/20 and 4/20, in the same order as above. No central nervous system (CNS) tumors developed, and all animals except one developed benign bronchial adenoma at a subpleural site. No other organ targets for tumor development were detected. Apparently, no CNS tropism occurs in mice under these experimental conditions. The question whether the organotropic action of MNU is species-, strain- or route of administration-determined is still to be resolved.

- 1591 *IN VITRO* TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS BY DIVERSE CHEMICAL CARCINOGENS. (E.) DiPaolo, J. A. (Natl. Cancer Inst., Bethesda, Md.), R. L. Nelson and P. J. Donovan. *Nature* 235(5336):278-280, 1972.

Experiments with Syrian hamster embryo cells were undertaken to determine whether classes of chemical carcinogens other than those such as polycyclic carcinogenic hydrocarbons or 4-nitroquinoline 1-oxide and its derivatives could produce *in vitro* transformation. Golden hamster embryo cells were minced and cultured. The test chemicals were added one day after cultured cells had been seeded for assay and eight days later treated colonies were fixed and examined for transformation. Test chemicals consisted of 11 compounds from seven classes of chemical carcinogen: aflatoxin B<sub>1</sub>, 11-methylcyclopenta(a)phenanthrene, N-2-fluorenylaceta-mide (FAA), N-hydroxy FAA, N-acetoxy FAA, urethan, N-hydroxyurethan, diethylnitrosamine (DEN), N-methyl-N'-nitro-N-nitrosoguanidine and methylazoxymethanol. Transformation was seen in cells from cultures treated with chemicals from five of the seven classes. The highest percentages of transformant cells were seen in cultures treated with N-acetoxy-AAF (15.4% transformants) and methylazoxymethanol (8.4% transformants). Urethan itself, N-hydroxyurethan and DEN failed to transform *in vitro*. However, when urethan or DEN was given i.p. to pregnant hamsters at day 12 of gestation, significant transformation was seen in cells of embryos removed on day 14 (17.9% transformants with DEN transplacental and 14.3% transformants with urethan transplacental). Thus, transformation by chemicals requiring *in vivo* activation could be demonstrated.

- 1592 VARIOUS N-METHYL-N-NITROSOUREA-INDUCED EFFECTS IN RATS: I. TUMORS. (Ger.) Kupfer, G. (Karl Marx U., Leipzig, Germany) and M. Kupfer. *Zbl Allg Path* 114(4):447-457, 1971.

The neurotropism of N-methyl-N-nitrosourea (MNU) was confirmed in Wistar male and female rats following combined i.v. and p.o. treatment. Sixty female rats were given a single 5 mg/kg MNU i.v. dose once per week and were then treated p.o., to a total of 220 mg/kg. Fifty percent of the rats in both groups were given 40-60 mg/kg caffeine along with each administration of MNU. Twenty-two of the 90 treated rats died before developing any detectable neoplasia. Of 68 tumor-bearing animals 21 had brain tumors, two had spinal cord neoplasms and 25 had peripheral neurinomas or neurosarcomas. Of the CNS tumors nine brain tumors were isomorphous gliomas, comparable to the human oligodendroglioma; seven were sarcomas and four were glioblastomas. Skin, mammary gland and the gastrointestinal tract appeared to be the sites for other neoplasms. Rats receiving a total of 220 mg/kg MNU developed tumors within 150-240 days, and those receiving a total of 150 mg/kg developed tumors within 170-380 days. Caffeine treatment produced no effects on the latency period, number and nature of the induced tumors. Experiments in progress with sheep and hogs have produced no detectable tumors from analogous treatment with MNU.

- 1593 CARCINOGENICITY OF 4-NITROQUINOLINE 1-OXIDE ANALOGS: PYRIDINE SERIES. (E.) Araki, M. (Natl. Cancer Ctr. Res. Inst., Sci. U. Tokyo, Japan), C. Koga, and Y. Kawazoe. *Gann* 62(4):325-327 (and Plate LXIV), 1971.

The carcinogenicity of 3-methyl-4-nitropyridine 1-oxide, a derivative of the pyridine series analogous to 4-nitroquinoline 1-oxide, is discussed. Female mice of the strain ddN were given s.c. injections in the right groin of various dilutions of 3-methyl-4-nitropyridine 1-oxide regularly once a week for 28 weeks. Eventually, nine of the mice developed tumors, one being a polymorphous cell sarcoma and the other eight being fibrosarcomas. Previous biochemical analysis of 4-nitropyridine 1-oxide, a noncarcinogen, and carcinogenic 4-nitroquinoline 1-oxide indicated that both are converted into 4-hydroxyamino derivatives by metabolic processes. However, 4-hydroxyaminoquinoline 1-oxide can be converted to a quinoid electronic structure by acylation, while 4-hydroxyaminopyridine 1-oxide yields a normal benzoid electronic structure. Subsequent introduction of an alkyl substituent to the pyridine molecule may alter the electronic structure of the corresponding hydroxyamino derivative from a benzoid to a quinoid type of structure, thus inducing tumor formation. The fact that the 3-methyl derivative of 4-nitropyridine 1-oxide did produce tumors at the site of injection may be a positive indication of the importance of a quinoid structure in the arylhydroxyamines.

- 1594 MORPHOLOGY OF HEART TUMORS INDUCED BY TREATMENT WITH NEUROTROPIC CARCINOGENS IN RATS. (Ger.) Mennel, H. D. (Max-Planck Inst. Brain Res., Cologne, Germany). *Beitr Path* 144(3):221-230, 1971.

The morphology of 17 heart tumors was studied in rats. Neoplasia was induced with ethylnitrosourea (ENU) administered p.o. to ten-day-old rats (10, 20, or 40 mg/kg single dose), i.v. to 30-day-old rats (20, 40 or 80 mg/kg single dose), or s.c. to 50-day-old animals (40 mg/kg single dose). One rat received chronic treatment with 2 mg/kg five times/wk with ENU, and other rats were given single doses of methylbenzylhydrazine or diethylnitrosamine in transplacental treatment (20 mg/kg s.c. and 150 mg/kg p.o., respectively, one or two days before birth). All tumors appeared to be a combination of highly differentiated tissue associated with wild sarcomatous portions. Two varieties of neoplasia could be distinguished: fast growing neurinoma-like entities, with features similar to those of the benign neurinoma and with still detectable regressive alterations in certain regions; and a sarcomatous variety. Both neoplastic varieties were comparable to experimentally induced malignant neurinomas in rats or spontaneous human neurinoma. Infiltrative growth and mitotic features emphasized the malignancy of the whole set of tumors studied. A discussion on specific organotropic and carcinogen structural relationships is included, but no explanation of the heart specific action under the given conditions is presented.



- 1595 ON THE ANALYSIS OF THE MUTAGENIC PROPERTIES OF A CARCINOGEN, 4-NITROQUINOLINE 1-OXIDE. (Jap.) Ishizawa, M. (Fac. Med., Kyushu U., Fukuoka, Japan). *Acta Med* 40(2):227-233, 1970.

The mechanism of the mutagenic effect of the carcinogen 4-nitroquinoline 1-oxide (4NQO) on bacteriophage T4 rII mutants was examined. In general, 4NQO does not affect phage particles directly; rather, it induces mutagenic effects when reacted with phage-infected cells. Three types of rII mutants with clear reversion tendencies, A-T, G-C, and frameshift, were exposed to the effect of 4NQO. Phage particles were incubated with or without 4NQO at a final concentration of 100 mg/ml in 0.1 M phosphate buffer containing 0.1 M NaCl, pH 7.2, at 37°C. Of the three types, only G-C type was affected by 4NQO and a reversion mutation was induced. It was confirmed that 4NQO had mutation effects only on intercellular phages, and that 4NQO was a point mutagen which induced G-C transition exclusively as far as rII mutations were concerned. From other reversion tests with 2-aminopurine, 5-bromodeoxyuridine, and hydroxylamine, it was confirmed that approximately 70% of rII mutants were induced by the transition of G-C to A-T; 30% were nontransition types. It was concluded that 4NQO predominantly induced a one-sided mutation of G-C to A-T. The suggestion was made that the mutation target of 4NQO might be the guanine or cytosine base group of the DNA molecule.

- 1596 REDUCED DNA REPAIR SYNTHESIS IN XERODERMA PIGMENTOSUM CELLS EXPOSED TO THE ONCOGENIC 4-NITROQUINOLINE 1-OXIDE AND 4-HYDROXY-AMINOQUINOLINE 1-OXIDE. (E.) Stich, H. F. (Cancer Res. Ctr., U. British Columbia, Vancouver, Canada) and R. H. C. San. *Mutat Res* 13(3):279-282, 1971.

Fibroblast cultures were obtained from a 20-year-old female xeroderma pigmentosum patient and from two healthy unaffected females aged 21 and 22 years. These cultures were subjected to UV irradiation or to 4-nitroquinoline 1-oxide, 4-hydroxyaminoquinoline 1-oxide, or N-methyl-N'-nitro-N-nitrosoguanidine in order to determine if DNA repair synthesis could occur after such carcinogenic and mutagenic exposures. By measuring the incorporation of tritiated thymidine into the DNA, it was found that xeroderma pigmentosum cells treated by 4-nitroquinoline 1-oxide, 4-hydroxyaminoquinoline 1-oxide, and UV irradiation showed reduced DNA synthesis when compared to normal cells. The chemical N-methyl-N'-nitro-N-nitrosoguanidine, however, had no effect. Hypotheses are presented concerning the cause of such reactions.

- 1597 TRANSFORMATION OF MAMMALIAN CELLS *IN VITRO* BY CHEMICAL CARCINOGENS. (Jap.) Sekiya, S. (Sch. Med., Chiba U., Japan), T. Kuwata and K. Nakamura. *Med Biol* 83(1):41-43, 1971.

The chemical carcinogen 4-nitroquinoline-1-oxide (4-NQO) was introduced into cultured cells of mouse, hamster and human fetuses, and cell transformation

was studied. Second passage cultured mammalian cells were treated with  $5 \times 10^{-6}$ M 4-NQO for four (mouse and hamster) or six (human) days. The cells were then washed with saline solution and cultured in the normal culture medium in order to show the effect of the drug. The cells from the mouse fetus stopped proliferating and showed some morphological changes at the end of the treatment. However, within the following three to four days, proliferation was resumed. No difference between the mode of proliferation and the morphology of the treated cells and those of the untreated cells was noted up to nine months (17th passage). The tissue cultured hamster fetus cells showed marked morphological changes and cell death within 24 hours after treatment. Most cells were detached from the glass surface of the petri dish. Approximately three weeks after treatment, some surviving cell colonies were observed, and the passage of culture was continued for about three months, at the end of which time morphologically distinct spindle-shaped cells became prominent. When the transformed cells were inoculated into the hamster, no tumors were produced. A successful induction of tumor was effected by inoculating four month old (230 days after 4-NQO treatment) transferred cells. No sign of transformation was observed in 4-NQO-treated human fetus cells up to five months, although their proliferation was slightly inhibited.

- 1598 ACCELERATION OF PROLIFERATION AND TUMOR PRODUCTION RATE OF L-STRAIN CELLS BY TREATMENT WITH CIGARETTE TAR. (E.) Inui, N. (Cancer Inst., Tokyo, Japan) and S. Takayama. *Cann* 62(4):315-320 (and plates LXI-LXIII), 1971.

Crude tar obtained from cigarette smoke was dissolved in ethanol to final concentrations of 500, 250, 100, and 25 µg/ml. The solutions of tar were placed on the L-cells only once for 3 + 0.2 hours at 37°C; control groups consisted of cells exposed for the same amount of time to various ethanol concentrations and of cells exposed to neither tar nor alcohol. When cells were treated with over 250 µg/ml of tar, most of them died of acute cytotoxicity within 24 hours after treatment. However, when the cells were exposed to 100 or 25 µg/ml of tar, they recovered from injuries four or five days after treatment and continued to grow for over 200 days *in vitro*. The tar-treated viable cells showed some biologic changes in character when compared with nontreated control cells. There was found to be: 1) an acceleration of growth rate appearing 50 to 60 days after treatment, with a concomitant shortening of the doubling time and an increase in plating efficiency; 2) a different chromosome number of treated cells from that of the controls, with no chromosome breakages or marker chromosomes observed; and 3) tumor production of the fibrosarcoma type caused by transplantation of infected cells into C3H strain newborn mice, with control cells showing no such development.

- 1599 FOOD AND DRUG ADMINISTRATION ADVISORY COMMITTEE ON PROTOCOLS FOR SAFETY EVALUATION: PANEL ON CARCINOGENESIS REPORT ON CANCER TESTING IN THE SAFETY EVALUATION OF FOOD

ADDITIVES AND PESTICIDES. (E.) Anonymous. *Toxic Appl Pharmacol* 20(3):419-438, 1971.

This report is concerned with the present status of testing for carcinogenic action of food additives and other chemicals which come into contact with man principally through his diet. In dealing with establishment of protocol for safety evaluation of food additives and pesticides, the following areas of concern are discussed: 1) basic research aspects of the problem; 2) discussion of updating testing procedures; 3) discussion of the questions: a) is the agent carcinogenic? and b) can a safe dose be found? 4) an outline of a broad general strategy of testing; and 5) recommendations and conclusions.

1600 INVESTIGATION OF THE POSSIBLE RELATIONSHIP BETWEEN ORAL CONTRACEPTIVES AND BENIGN AND MALIGNANT BREAST DISEASE. (E.) Vessey, M. P. (U. Coll. Hosp. Med. Sch., London, England), R. Doll and P. M. Sutton. *Cancer* 28(6):1395-1399, 1971.

To determine whether the use of oral contraceptives would increase the risk of breast neoplasia, 166 women suffering from benign mammary tumors and 54 women suffering from malignant breast growths were interviewed about their obstetrical, menstrual, and contraceptive history. Those patients with breast disease, aged 16 to 39 years, were matched with normal control women. It was found that oral contraceptives are not associated with an increased risk of breast cancer; on the contrary, these steroids may protect women against benign lesions. However, the data concerning the brand of oral contraceptive could not be correlated since half the women took more than one preparation and 18 separate products were represented throughout the entire group of patients. Further analyses of the data will be carried out and published at a later date.

1601 PHYSICOCHEMICAL AND OTHER FACTORS DETERMINING LOCAL SARCOMA PRODUCTION BY FOOD ADDITIVES. (E.) Grasso, P. (Brit. Indust. Biol. Res. Ass., Carshalton, Surrey, England), S. D. Gangolli, L. Golberg and J. Hooson. *Fd Cosmet Toxicol* 9(4):463-478, 1971.

It was found previously that repeated s.c. injections of water-soluble food colorings and other selected compounds into rats causes reactions dependent on the lipophilic properties of the injected substances. These reactions were divided into four classes: Type I was a mild reaction in connective tissue; Type II was called a moderately severe reaction and was also limited to connective tissue; a Type III reaction consisted of intense macrophage response; and a Type IV reaction was characterized by the local deposition of collagen and fibroblastic proliferation. These reactions are considered in this study as an indicator of possible tumor production caused by food additive agent injections into rats. Physicochemical studies were done on the agents to be injected - the food additives Blue VRS, Patent Blue V, Tween 80, and sodium and calcium salts of cyclohexylsulphamic acid.

Shell or Carworth albino rats of strain E were then subjected to single s.c. biweekly injections of these agents. Calcium cyclamate caused a Type IV reaction in connective tissue with subsequent formation of local sarcomas, while sodium cyclamate showed no tissue destruction and no tumorous growths. Tween 80 caused a Type III tissue reaction, with tumor formations occurring in half the injected animals. Blue VRS and Patent Blue V both showed Type IV destruction of the tissue and both had a considerable influence on local tumor production. All the tumors that developed were found to be fibrosarcomas, ranging from well differentiated forms to poorly differentiated structures. The development of local tumors was prevented, however, when test compounds were given in relatively dilute solutions. A correlation appeared between the progressively intensifying lesion induced in the short-term tests and the eventual development of sarcomas. Physicochemical factors, unrelated to any specific chemical structure, determine both the tissue reaction and the ultimate evolution of sarcomas. In the authors' discussion the observations are finally examined in the light of previous publications.

1602 BLASTOMOGENICITY OF NEUTRALIZED SOOTS FROM THE SULFATE SHOP OF A COKE PLANT. (Rus.) Shustova, M. N. (Grozhenk Sanitary Epid. Center, USSR) and L. N. Samoilovich. *Gig Sanit* 36(7):103-104, 1971.

The basic constituents of neutralized soot used in highway construction are aromatic compounds, naphthalene and anthracene; heterocyclic compounds, phenols, cresols, thiophene, thionaphthene, pyridine, carbazole and pyrrole. The naphthalene and phenol contents are 4% and 3%, respectively. Experiments were carried out on 50 C57Bl x CBA hybrid mice to investigate the possible carcinogenic effect of neutralized soot. The substance was diluted with benzene and applied to the depilated skin on the interscapular region of the back thrice a week for ten months. Benzene was applied on a control group. Hyperkeratosis and papillomatous neoplasia were observed in three test animals after three months. Papillomatosis was found in 50% of the test animals in the fifth month. Neoformations of 2-2.5 mm were observed in all test animals after six months, while only alopecia and thinning hair were found in the control group. Deaths occurred in the test group due to malignant neoformations as of the third month. Squamous carcinoma was observed in 27 cases, papilloma with keratosis and beginning malignant degeneration in ten cases, and skin sarcoma in one case. Skin lesions were accompanied by metastasis of squamous epithelioma without keratinosis and with bronchial keratinization in four cases. The fluorescent spectrophotometric analysis of the neutralized soot revealed a 3,4-benzopyrene content of 94,157 µ/kg.

1603 TRANSPLACENTAL BLASTOMOGENESIS IN ORGAN CULTURES OF EMBRYONIC LUNG TISSUE. (E.) Shabad, L. M. (USSR Acad. Med. Sci., Moscow), T. S. Kolesnichenko, and E. Y. Smetanin. *J Nat Cancer Inst* 47(5):987-1005, 1971.



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- 1606 HISTOLOGY OF PRENEOPLASTIC ALTERATIONS IN RAT CEREBELLUM FOLLOWING ADMINISTRATION OF 9,10-DIMETHYL-1,2-BENZANTHRACENE. (Rus.) Avtsyn, A. P. (Inst. Hum. Morphol., Moscow, USSR) and L. Ya. Yablonovskaya. *Biull Eksp Biol Med* 72(8):96-99, 1971.
- 1607 TRANSPLACENTAL ONCOGENICITY OF DIMETHYL-NITROSAMINE AND NITROSOMETHYLUREA. (Rus.) Smetanin, E. Ye. (USSR Acad. Med. Sci., Moscow). *Vop Onkol* 17(8):75-81, 1971.
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- 1630 EFFECTS OF ACTINOMYCIN D AND PUROMYCIN ON THE CELL PROGRESS FROM M TO G<sub>1</sub> AND S STAGES IN CULTURED MOUSE LEUKEMIA L5178Y CELLS. (E.) Doida, Y. (U. Rochester Med. Ctr., N. Y.) and S. Okada. *Cell Tissue Kinet* 5:15-26, 1972.
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- 1635 FURTHER ULTRASTRUCTURAL OBSERVATIONS ON INJURY OF RAT HEPATIC PARENCHYMAL CELLS INDUCED BY AFLATOXIN B<sub>1</sub>. (E.) Butler, W. H. (Med. Res. Council Lab., Carshalton, England). *Chem Biol Interact* 4(1):49-65, 1971-72.
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- 1637 RELATIONSHIP BETWEEN CIGARETTE SMOKING AND HIGH PACKED CELL VOLUME AND HAEMOGLOBIN LEVELS. (E.) Isager, H. (Centofte Hosp., Copenhagen, Denmark) and L. Hagerup. *Scand J Haemat* 8(4):241-244, 1971.
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- 1641 THE PRESENCE OF DELAYED HYPERSENSITIVITY REACTIONS IN PATIENTS TOWARD CELLULAR EXTRACTS OF THEIR MALIGNANT TUMORS: 3. THE FREQUENCY, DURATION AND CROSS REACTIVITY OF THIS PHENOMENON IN PATIENTS WITH BREAST CANCER, AND ITS CORRELATION WITH SURVIVAL. (E.) Stewart, T. H. M. (Dept. Med., U. Ottawa, Canada) and M. Orizaga. *Cancer* 28(6):1472-1478, 1971.



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- 1646 THE EFFECT OF METHYL METHANESULPHONATE ON THE LEVELS OF HEPATIC GLYCOGEN IN THE RAT. (E.) Pillinger, D. J. (Paterson Lab., Christie Hosp., Manchester, England). *Life Sci* 10(2):1405-1414, 1971.
- 1647 SOME STUDIES ON THE PHOTOLYTIC DECOMPOSITION STAGE IN THE ESTIMATION OF *N*-NITROSAMINES. (E.) Burns, D. T. (U. Tech. Loughbrough, England) and G. V. Alliston. *J Fd Technol* 6(4):433-438, 1971.
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- 1650 A COMPARISON OF THE EFFECTS OF BENZPYRENE ADMINISTRATION ON SOME HEPATIC MICROSOMAL MIXED-FUNCTION OXIDASES OF RATS AND MICE. (E.) Hansen, A. R. (Coll. Med., U. Iowa, Iowa City) and J. R. Fouts. *Biochem Pharmacol* 20:3125-3143, 1971.
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- 1655 A COMPARATIVE ULTRASTRUCTURAL STUDY ON DRUG-INDUCED PROLIFERATION OF SMOOTH-SURFACED ENDOPLASMIC RETICULUM IN HEPATOCYTES. (E.) Garg, B. D. (Inst. Med., U. Montreal, Quebec, Canada), J. A. Blascheck and K. Kovacs. *Tohoku J Exp Med* 104(3):205-214, 1971.

See also:

- \* (Rev): 1504, 1505, 1511, 1513
- \* (Phys): 1661
- \* (Viral): 1728, 1730, 1731
- \* (Immun): 1815, 1816, 1821, 1826, 1876
- \* (Path): 1888
- \* (Epid-Biom): 1922

- 1656 MALIGNANT LYMPHOMA. (E.) Anderson, R. E.  
(U. New Mexico Sch. Med., Albuquerque).  
*Hum Path* 2(4):515-519, 1971.

Data from the Atomic Bomb Casualty Commission, Hiroshima, Japan, were analyzed to determine whether a correlation exists between prevalence of malignant lymphoma in nuclear bomb blast survivors and distance of survivors from the explosion hypocenter. The relationship between lymphoma incidence and estimated total dose of radiation sustained by survivors was also explored; 682 cases of lymphoma were examined. Available evidence suggested an increased prevalence of malignant lymphoma in highly exposed ( $> 100$  rads) Hiroshima survivors as compared to those not in Hiroshima during the bombing attack. Males less than 25 years old at the time of the Hiroshima explosion who were within 1499 m of the explosion hypocenter were particularly susceptible to malignant lymphoma. The incidence of Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and multiple myeloma in highly exposed Hiroshima survivors also increased. Similar correlations between radiation and development of lymphosarcoma and related conditions were not evident in the population of Nagasaki. It was hypothesized that this was due to differences in the radiation spectra of the Hiroshima and Nagasaki bombs, and/or to genetic differences in the populations of the two cities.

- 1657 CARCINOMA OF THE PROSTATE. (E.) Jordan, S. W. (U. New Mexico Sch. Med., Albuquerque).  
*Hum Path* 2(4):539, 1971.

Carcinoma of the prostate with metastases has shown no differential prevalence rate among the various exposure categories of atomic bomb survivors and non-irradiated age-matched patients. Preliminary results of a search for occult prostatic carcinoma involving examination of multiple sections of the prostate from the Hiroshima and Nagasaki autopsy series indicate no differences in prevalence rates among atomic bomb exposed subjects at varying distances from hypocenter and age-matched non-exposed subjects. A high prevalence rate of occult prostatic carcinoma in men 80 years old and older was found.

- 1658 ACTIONS OF RADIATIONS ON HUMAN CHROMOSOMES. (E.) Evans, H. J. (Western Gen. Hosp., Edinburgh, Scotland). *Phys Med Biol* 17(1):1-13, 1972.

Chromosome aberrations caused by ionizing radiation appears to be due to breakage of chromosomes with abnormal rejoining of the broken ends either within a chromosome (intrachange) or between chromosomes (interchange). The number of such aberrations is directly related to several factors, some of which are radiation dose, type of radiation, and dose rate. In addition, biological factors such as age at time of exposure, genetic constitution, and general health also affect the ultimate chromosome aberration yield after radiation exposure. The biological consequences of such irradiation chromo-

some damage are hard to estimate in any individual, but attempts are now being made *in vivo* and *in vitro* to predict the relation of gene damage to somatic cell and reproductive cell behavior.

- 1659 ANTIGENIC CHANGES IN DYSPLASIA AND NEOPLASIA FOLLOWING X-IRRADIATION OF RODENT GASTRO-INTESTINAL TRACT. (E.) De Boer, W. G. R. M. (Monash U. Med. Sch., Melbourne, Australia) and M. N. Cauchi. *Pathology* 3(4):291-296, 1971.

Antigenic changes which occurred in irradiation-induced dysplasia and neoplasia within the gastro-intestinal tract of rodents are reported. Fifty strain CSL mice were given 1000 rads of irradiation to the stomach in a single exposure, a second group of 50 received the same dose to exteriorized colon, a third group of 50 was held as control. Ten Lister hooded rats were given 1,000 rads irradiation to the stomach and a like group was held as controls. Following irradiation, 23 mice and five rats died. From surviving animals, two mice were killed every four weeks for a 12 month period. Mice showed mild localized loss of normal cell architecture, some depletion of mucin, but no tumors. Of five surviving rats macroscopic tumors were found in two; the remaining three showed presence of infiltrating carcinoma when histologically examined. Immunofluorescence studies on tissues revealed: 1) loss of gastric-specific antigen in dysplastic areas of irradiated mouse stomach, as well as in metaplastic and neoplastic areas in rat stomach, 2) gain of intestinal-specific antigen in irradiated tissue, and 3) displacement and loss of parietal cells. The loss of gastric antigen and gain of intestinal-specific antigen is interpreted as evidence of cytogenetic lability which eventually leads to malignant transformation.

- 1660 SALIVARY GLAND TUMORS IN ATOMIC BOMB SURVIVORS, HIROSHIMA-NAGASAKI, 1957-1970. (E.) Belsky, J. L. (Atomic Bomb Casualty Commission, Hiroshima, Japan), K. Tachikawa, R. W. Chiak and T. Yamamoto. *JAMA* 219(7):864-868, 1972.

A study of 109,000 subjects, of whom approximately 82,000 were survivors exposed to various levels of radiation in Hiroshima and Nagasaki in 1945, was undertaken to determine whether salivary gland tumor incidence was increased in the survivor group; data in the period 1957 to 1970 were analyzed. Four dose categories were used: 1) no exposure (zero rads); 2) 1 to 89 rad; 3) 90 to 299 rad; and 4) 300+ rad. In an analysis of 22 proven salivary gland tumors among the survivors, 14 were found to be benign, eight malignant. Characteristics typical of mixed salivary gland tumors were found in 15 of the tumors. Consideration by radiation dose group for all 22 cases showed that salivary gland tumor incidence increased with increasing exposure to radiation. Irradiated salivary gland tumor subjects had a mean age at exposure of 26 years for 1-89 rads, 26.5 years for 90-299 rads, and 26 years for 300+ rad, as compared to 32.4 years for nonirradiated salivary gland tumor subjects. A-bomb survivors exposed to higher doses of radiation had a greater chance of having salivary gland tumors than



those not irradiated. No definite conclusions could be made regarding possible different tumorigenic effects of high and low radiation doses. It is suggested that a younger age at exposure produces higher susceptibility to radiation-induced salivary gland tumors.

1661 X-IRRADIATION ENHANCEMENT OF TRANSFORMATION BY BENZO(a)PYRENE IN HAMSTER EMBRYO CELLS.

(E.) Dipaolo, J. A. (Natl. Cancer Inst., Bethesda, Md.), P. J. Donovan and R. L. Nelson. *Proc Nat Acad Sci USA* 68(8):1734-1737, 1971.

Hamster cells, either irradiated or nonirradiated, were plated on a feeder layer of rat embryo cells. At designated intervals from six to 72 hours after irradiation, benzo(a)pyrene (BP) was added to the cultures to final concentrations of 2.5 or 10 µg/ml of medium. Plates were studied over an eight-day period; irradiation of hamster cells significantly enhanced transformation of cells by BP. Optimal doses of BP (zero to 500 R) plus addition of carcinogen up to 48 hours after irradiation increased the transformation capacity of the hamster cells. However, too much radiation (over 500 R), or delaying the addition of BP to 72 hours or more postirradiation, resulted in small or no increased enhancement of transformation.

1662 STUDIES OF THE MORTALITY OF A-BOMB SURVIVORS: 4. MORTALITY AND RADIATION DOSE, 1950-1966.

(E.) Beebe, G. W. (Natl. Inst. Hlth Japanese Ministry Hlth. Welfare, Atomic Bomb Casualty Commission, Japan), H. Kato and C. E. Land. *Radiat Res* 48(3):613-649, 1971.

This study includes 9,500 Nagasaki and Hiroshima A-bomb survivors in addition to 99,500 previously reported, and provides a re-analysis of the survivors as well as the 16,536 deaths from 1950 to 1966 resulting from exposure to the A-bomb. This analysis is made on the basis of age at the time of the bomb (ATB), sex, city of exposure, calendar time, underlying cause of death, dose according to new T-65 estimates and distance from the hypocenter ATB. The results are compared to those from a control survivor group not in Nagasaki or Hiroshima ATB. The mortality increase in the high-radiation dose groups over the 16-year study period was due primarily to an increase in the incidence of leukemia from 200 to 800% over the expected death rate from that cause. Two thirds of all deaths due to malignancies other than leukemia were caused by cancers of the digestive organs and peritoneum (78% in males and 56% in females). There was no evidence for association of these cancers with dosage in the periods of 1954-1958 and 1958-1962, but in 1962-1966 the test for linear trend on all Hiroshima subjects was positive. That for Hiroshima females was borderline ( $P=0.05$ ). For the entire 16-yr period, incidence of cancer of the respiratory system in Hiroshima males showed a significant relation to dosage ( $P<0.05$ ). Relationships suggesting a correlation between radiation dose and respiratory tumors was also seen for Nagasaki males ( $P=0.09$ ) and for Hiroshima females ( $P=0.07$ ). The greatest evidence for this correlation was seen for age cohorts 40-49 and 50-59 ATB for the

1962-1966 period. During the 16-yr time period of this study, a rather strong association of anemias and other hematopoietic diseases with T-65 dose was seen in all four city-sex groups. Unlike deaths from leukemia, which declined from 16 to 25. They also showed an older age distribution ATB than was characteristic of leukemia. The most significant finding of this study was the general increase of deaths of A-bomb survivors due to all types of cancers from 1962-1966; a carcinogenic effect may therefore have become generalized. Examination of mortality rates from all natural causes except malignancies provided no support for the hypothesis that ionizing radiation accelerates the aging process in man.

1663 LEUKEMIA AND RELATED DISORDERS. (E.)

Anderson, R. E. (U. New Mexico Sch. Med., Albuquerque). *Hum Path* 2(4):505-514, 1971.

One of the delayed consequences of exposure to significant amounts of ionizing radiation is the development of leukemia; this has been amply demonstrated by studies on atomic bomb explosion survivors from Hiroshima and Nagasaki, Japan. Analysis of data collected by the Atomic Bomb Casualty Commission (ABCC) shows all forms of leukemia, particularly the myelogenous type, increased in prevalence in the proximally located survivors, especially in those that suffered serious radiation sickness. A pronounced increased incidence of myelogenous leukemia was noted in exposed males and in children ranging from zero to 19 years of age at the time of exposure, with the minimum time for evolution of neoplastic blood disease being less than three years. Myelofibrosis was also found to be related to radiation exposure, thus demonstrating an inverse relationship between distance and prevalence. However, polycythemia rubra vera, thrombocytopenia, erythremic myelosis, and erythroleukemia all seem unrelated to radiation overdose, although these diseases may have a longer latency period than myelofibrosis and myelogenous leukemia. The data available was found neither to support nor to refute the concept of threshold dose and does not imply any clinical difference between spontaneous and radiation-related leukemia.

1664 ACUTE MYELOGENOUS LEUKEMIA FOLLOWING LOCALIZED RADIOTHERAPY. (E.) Poth, J. L.

(Sch. Med., Stanford U., Calif.), R. P. George, Jr., W. P. Creger and S. L. Schrier. *Arch Intern Med* 128(5):802-805, 1971.

A report on four patients who developed acute myelogenous leukemia following localized radiotherapy is presented. Each patient was given a minimum of 2,900 rads localized radiotherapy for neoplastic disease and each developed acute myelogenous leukemia in 32 months to ten years following treatment. At autopsy no evidence of the original tumor for which the patient had been treated was found in three of the four patients. It is suggested that a higher frequency of leukemia may occur in patients with various neoplasms who receive high doses of radiation in the course of treatment.

- 1665 COMPARTMENTS OF LEUKAEMOGENIC RESPONSE TO RADIATION. (E.) Ilbery, P. L. T. (Sch. Pub. Hlth., U. Sydney, New South Wales, Australia). *Nipp Acta Radiol* 31(4):331-339, 1971.

A cytogenetic study of 100 female C57BL mice with radiation-induced leukemia is reported. Of 100 radiation-induced leukemias, 88 showed cells with abnormal classes of chromosome sets. Post-radiation treatment with lymphoid material, including whole lymph node grafts placed beneath the kidney capsule, showed no effect on the incidence of radiation-induced leukemia; however, shielding the lower abdominal wall during radiation, and thereby preserving a small amount of lymphoid material, was effective. Results showed that with increasingly larger final increments of whole-body radiation the incidence of leukemia decreased; 66 of 100 mice given 200 rads died of leukemia, while none of 26 mice given 800-1100 rads died of leukemia. Death due to aplastic anemia increased with increasing radiation dose. The unexplained peaking of leukemia induction at 200 days post-infection was thought to be due to activation of a latent virus. It was thought that prevention of radiation-induced leukemia may have depended on the availability of a nonirradiated bone marrow-derived cell which restored thymic competence in treated animals.

- 1666 STUDIES ON HEMATOLOGIC CHANGES AFTER ADMINISTRATION OF THERAPEUTIC DOSIS OF RADIOACTIVE IODINE: II. CHANGES OF THE PERIPHERAL BLOOD AND BONE MARROW AFTER RADIOACTIVE IODINE THERAPY FOR HYPERTHYROIDISM. (Jap.) Nakayama, S. (Kyoto U., Sch. Med., Japan). *Acta Haematol Jap* 33(5):578-597, 1970.

A long-term observation was made on the effects of  $I^{131}$  on hematopoietic organs and on the blood and bone marrow that could possibly lead to development of leukemia. After the initiation of treatment of hyperthyroid patients with  $I^{131}$ , a decrease of peripheral lymph cells and neutrocytopenia, and a temporary decrease of thrombocytes, were noted quite early. The number of neutrocytes returned to normal in two months, increasing gradually after that. Lymph cells were below the initial level even five years after treatment. There was no correlation between the rate of initial decrease of cells and dosage of  $I^{131}$  and between that and bone marrow radiation dose. The area index of platelet of erythrocyte, hemoglobin content, mean lobe count of neutrophil, and Al-P activity of neutrophil remained within the limits of normal fluctuation after  $I^{131}$  treatment. Relative lymphocytosis and mutation arrest were recognized in the bone marrow two to five days after administration of  $I^{131}$  as a reaction caused by the  $\beta$ -ray. However, with normalization of thyroid function, nucleated cells in the bone marrow decreased and improvements appeared in the lymph cell percentage, formation of granule cells, and maturation process. In the course of hypofunction of thyroid during the treatment, a clear sign of hypoplasia of bone marrow was recognized, which could potentially transform into leukemia. These phenomena in the peripheral blood and bone marrows in thyroid patients indicate a high suscepti-

bility of radiation, and hematologic transitions after  $I^{131}$  treatment do not necessarily signify a direct progress toward leukemia. However, individuals who are highly susceptible to radiation should consider that possibility before receiving treatment.

- 1667 STUDIES ON HEMATOLOGIC CHANGES AFTER ADMINISTRATION OF THERAPEUTIC DOSIS OF RADIOACTIVE IODINE: I. STATISTICAL STUDIES ON THE OCCURRENCE OF LEUKEMIA. (Jap.) Nakayama, S. (Kyoto U. Sch. Med., Japan). *Acta Haematol Jap* 33(5):560-577, 1970.

A followup examination of 3666 hyper-thyroid patients treated with  $I^{131}$  revealed that two cases of leukemia had occurred. This statistic was 0.4 person above the average leukemia occurrence for the same number of post therapeutic patients during an average five-year followup period. However, a significant conclusion could not be drawn from this data due to the limited number of cases. Analyses were attempted for the 42 cases of leukemia which followed  $I^{131}$  treatments and which have been reported in Japanese and foreign publications, with the following characteristics being found. The average bone marrow and blood radiation doses of  $\beta$ - and  $\gamma$ -rays from  $I^{131}$  treatment for hyperthyroidism are  $17.9 \pm 16.6$  rads and  $22.43 \pm 20.5$  rads. The doses for the treatment of thyroid cancer were 686 rads and 945 rads, respectively. The leukemia cases reported were all acute, and the rate of occurrence of acute myelogenous and aleukemic origins was extremely high. The latent period between the administration of  $I^{131}$  and the onset of leukemia ranged between two and five years. These symptoms are similar to the characteristics of leukemia occurring after radiotherapy. Cases of continuous leucopenia and delayed thyroid malfunction after  $I^{131}$  administration are numerous, and the ratio is high among male patients of the advanced age group. Further long-term epidemiologic and clinical-pathologic studies will be necessary in order to determine the effects of a relatively low dosage of  $I^{131}$  therapy.

- 1668 NUCLEAR CHANGES DURING ULTRAVIOLET LIGHT-INDUCED DEPRESSION OF RIBONUCLEIC ACID AND PROTEIN SYNTHESIS IN HUMAN EPIDERMIS. (E.) Wier, K. A. (Dept. Derm., U. California, San Francisco, ), K. Fukuyama and W. L. Epstein. *Lab Invest* 25(5):451-456, 1971.

This study examines the ultrastructure of the nucleus of human epidermal cells during the time of depressed RNA, DNA, and protein synthesis and presumed dark repair of DNA observed *in vivo* following ultraviolet irradiation. Skin biopsies were taken from covered lower back of six volunteers at three and six hours after irradiation with three minimal erythema doses ( $8.2-40.8 \times 10^6$  ergs per  $cm^2$ ) of mixed ultraviolet light and from nonirradiated control sites. One-half of each specimen was fixed in phosphate-buffered glutaraldehyde followed by postfixation in  $OsO_4$  and these results were compared with the other half, fixed in *s*-collidine-buffered  $OsO_4$ . Thin sections were stained with uranyl acetate and lead citrate with and without ethylenediaminetetraacetate extraction to remove



chromatin. The results at three hours showed with both fixations that almost all nucleoli had a variable degree of fragmentation and/or clumping of the nucleolonemal pattern. Electron-dense clumps appeared in the nucleus of the *s*-collidine-OsO<sub>4</sub>-fixed tissue on the background of the homogeneous granular pattern seen in control nuclei. At six hours with both fixations segregation of the fibrillar and granular components of the nucleoli became obvious in many cells, while nuclear coiled bodies showed no change. Scattered cells showed shrunken, densely stained, vacuolated and disorganized nuclei and cytoplasm. These findings represent the earliest morphologic changes occurring after ultraviolet light irradiation in human epidermis *in vivo* and may relate to decreased RNA and protein synthesis.

- 1669 ANEMIC STRESS AS A TRIGGER OF MYELOGENOUS LEUKEMIA IN RATS RENDERED LEUKEMIA-PRONE BY X-RAY. (E.) Gong, J. K. (Sch. Dent. State U. New York, Buffalo). *Science* 174(4011): 833-835, 1971.

The observation that prolonged anemic stress in irradiated animals could result in abnormally severe and uncontrolled granulocytosis, essentially myelogenous leukemia, was evaluated through this study. One to three months after two groups of female Sprague-Dawley rats were subjected to various levels of irradiation two thirds of the blood volume was bled within a 24 hour period. Control animals were either not irradiated or bled, irradiated and not bled, or maintained in an untreated condition. All irradiated and bled mice died of complications associated with the terminal phase of myelogenous leukemia: pneumonia, anemia, and inanition. The survival time in these animals was found to be a complex function of x-ray dose and time when bled after irradiation; neoplastic incidence was proportional to the x-ray dose given. Some (6%) of the irradiated and not bled animals also developed myelogenous leukemia, probably because the x-ray dose induced anemia which in turn mimicked the bleeding procedure and resulted in the neoplastic symptoms. However, none of the untreated or not irradiated and bled mice contracted leukemia. It is suggested that leukemogenesis involves a two-step process: first, the x-ray renders the subject leukemia-prone, and second, the anemia triggers the actual disease.

- 1670 THE INITIAL EFFECT OF X-RADIATION ON THYMIDINE INCORPORATION INTO DNA IN THYMUS CELLS. (E.) Myers, D. K. (Atomic Energy Canada, Ltd., Chalk River, Ontario). *Radiat Res* 47(3):731-740, 1971.

- 1671 PROLIFERATIVE ACTIVITY OF THE BLOOD-FORMING TISSUES UNDER THE CONDITIONS OF EXPERIMENTAL CHRONIC GAMMA-RAY IRRADIATION. (Ger.) Belousova, O. I. (No affiliation) and M. I. Fedotova. *Rad Biol Ther* 12(2):243-250, 1971.

- 1672 ON SOME REGULARITIES OF THE CHANGE OF THE LYMPHOCYTIC COUNT IN THE PERIPHERAL BLOOD AND IN THE BONE-MARROW OF RATS IN THE EARLY STAGE OF RADIATION SICKNESS. (Ger.) Gruzdev, G. P. (No affiliation) and E. N. Scerbova. *Rad Biol Ther* 12(2): 251-255, 1971.

- 1673 THYROID CARCINOMA FOLLOWING IODINE-131 THERAPY: REPORT OF A CASE AND REVIEW OF THE LITERATURE. (E.) McDougall, I. R. (Royal Infirm., Glasgow, Scotland), J. S. Kennedy and J. A. Thomson. *J Clin Endocr* 33(2):287-292, 1971.

- 1674 LATE SOMATIC EFFECTS IN RATS TREATED WITH 2- $\beta$ -AMINOETHYLISOTHIOURONIUM-Br-HBr AND EXPOSED OR NOT TO X-IRRADIATION. (E.) Fridman-Manduzio, A. (Inst. Path., U. Liege, Belgium), J. R. Maisin, A. Leonard and G. Mattelin. *Strahlentherapie* 142(1):80-87, 1971.

- 1675 EFFECTS OF X-IRRADIATION ON TISSUE FORMATIVE ACTIVITY AND SORTING-OUT ACTIVITY OF HeLa CELLS IN ROTATION CULTURE. (E.) Kuroda, Y. (Natl. Inst. Genet., Misima, Japan). *Radiat Res* 48(3):565-577, 1971.

- 1676 INDUCTION OF UNSCHEDULED DNA SYNTHESIS BY HALF-NUCLEUS IRRADIATION OF HELA CELLS WITH AN UV-MICROBEAM IN COMBINATION WITH HYDROXYUREA TREATMENT. (E.) Yatani, R. (Mie Prefectural U. Sch. Med., Tsu, Japan). *Mie Med J* 20(2):93-104, 1970.

- 1677 STUDIES ON THE BIOLOGICAL EFFECT OF SMALL DOSES OF IONIZING RADIATION. (E.) Rudnicki, T. (Med. Acad., Poznan, Poland), and B. Sloninska. *Acta Physiol Pol* 21(6):661-668, 1970.

- 1678 DOSE AND TIME DEPENDENCE OF RADIATION-INDUCED CHROMOSOMAL ABERRATIONS IN RAT EMBRYOS: I. IRRADIATION DURING ORGANOGENESIS. (Ger.) Eicke, J. (Radiobiol. Inst., U. Munich, Germany) and O. Hug. *Biophysik*, 7(4):322-341, 1971.

- 1679 RADIATION RECOVERY OF LONG-LIVED LYMPHOCYTES IN THE RAT. (E.) Benninghoff, D. L. (Downstate Med. Ctr., Brooklyn, N.Y.), R. Girardet and L. Stackhouse. *Radiat Res* 48(3): 589-598, 1971.

- 1680 RADIONUCLIDE CARCINOGENESIS AND SINUS CARCINOMA. (E.) Rubin, P. (No affiliation). *JAMA* 219(3):354-355, 1972.

- 1681 DELAYED HAZARDS OF RADON IRRADIATION. (E.) Camiel, M. R. (St. U. New York, Brooklyn) and D. Thompson. *JAMA* 219(3):384, 1972.

- 1682 THE PATHOLOGIST AND IONIZING RADIATION.  
(E.) Angevine, D. M. (Armed Forces Inst. Pathol., Washington, D.C.). *Hum Path* 2(4):467-468, 1971.
- 1683 REVERSIBLE ALTERATIONS OF NUCLEIC ACID SYNTHESIS IN LYMPHOCYTES AFTER THERMAL BURNS. (E.) Sakai, H. (U. Texas Med. Branch, Galveston), J. C. Daniels, S. R. Lewis, J. B. Lynch, D. L. Larson and S. E. Ritzmann. *J Reticuloendothel Soc* 11:19-28, 1972.
- 1684 ABERRANT RECOVERY OF PROTEIN SYNTHESIS AFTER MASSIVE IRRADIATION OF *Arachis hypogaea*, L. CELLS IN VITRO. (E.) Verma, D. P. S. (Dept. Plant. Sci., U. Western Ontario, Canada) and R. B. van Huystee. *Radiat Res* 48(3):531-541, 1971.
- 1685 NASCENT DNA SYNTHESIS IN ULTRAVIOLET LIGHT-IRRADIATED MOUSE L CELLS. (E.) Chiu, S. F. H. (Ontario Cancer Inst. U. Toronto, Canada) and A. M. Rauth. *Biochim Biophys Acta* 259(2):164-174, 1972.
- 1686 EVALUATION OF TUMOR INCIDENCE FOLLOWING EXPOSURE TO INTERNAL EMITTERS BY APPLICATION OF THE LOGISTIC DOSE-RESPONSE SURFACE. (E.) Rosenblatt, L. S. (Radiobiol. Lab., U. California, Davis), N. H. Hetherington, M. Goldman and L. K. Bustad. *Health Phys* 21(6):869-875, 1971.
- 1687 ATOMIC BOMB CANCER MORTALITY IN JAPAN. (E.) Jablon, S. (Atomic Bomb Casualty Commission, Hiroshima, Japan), J. L. Belsky, K. Tachikawa and A. Steer. *Modern Med* 39(26):101, 1971.
- 1688 CANCER FOLLOWING TREATMENT OF AN AUTONOMOUSLY FUNCTIONING THYROID NODULE WITH SODIUM IODIDE I 131. (E.) Hamburger, J. I. (Northland Thyroid Lab., Southfield, Mich.) and D. A. Meier. *Arch Surg* 103(6):762-764, 1971.
- 1689 AN AUTONOMOUSLY FUNCTIONING THYROID NODULE, CANCER, AND PRIOR RADIATION: CASE REPORT AND HYPOTHESIS. (E.) Meier, D. A. (Northfield Thyroid Lab., Southfield, Mich.) and J. I. Hamburger. *Arch Surg* 103(6):759-761, 1971.
- 1690 FIBROSARCOMA OCCURRING AT THE SITE OF A PLASTIC VASCULAR GRAFT. (E.) Burns, W. A. (VA Hosp., Washington, D.C.), S. Kanhouwa, L. Tillman, N. Saini and J. B. Herrmann. *Cancer* 29(1):66-72, 1972.
- 1691 LUNG CANCER AMONG POPULATIONS HAVING LUNG IRRADIATION. (E.) Axelsson, O. (Regional Hosp., Orebro, Sweden) and M. Rehn. *Lancet* (7740): 46-47, 1972.

See also:

- \* (Chem): 1639
- \* (Viral): 1707
- \* (Epid-Biom): 1928, 1937



# VIRAL CARCINOGENESIS

- 1692 STUDIES ON THE PRESENCE OF PARTICLES RESEMBLING RNA VIRUS PARTICLES IN HUMAN BREAST TUMORS, PLEURAL EFFUSIONS, THEIR TISSUE CULTURES, AND MILK. (E.) Seman, G. (U. Texas M. D. Anderson Hosp. Tumor Inst. Houston), H. S. Gallager, J. M. Lukeman and L. Dmochowski. *Cancer* 28(6):1431-1442, 1971.

Ultrastructural studies were performed on biopsies of 84 breast cancers, 13 metastatic lymph nodes, three fibroadenomas, and on cells from 33 pleural effusions from breast cancer patients. Breast tumor and pleural effusion cells resembled mesothelial cells in that they were characterized by lobulated and frequently multiple nuclei, enlarged nucleoli, enlarged and sometimes giant mitochondria containing bundles of tubular structures, and duct-like cytoplasmic vacuoles bordered by microvilli. Particles resembling both mouse mammary tumor (type B) and murine leukemia (type C) viruses were observed in 34 of the biopsies and in two of the pleural effusion specimens. Small 300 to 500 Å virus-like particles were also found as cytoplasmic inclusions and in the extracellular spaces of 26 breast cancer specimens; other "trace" particles included hamster virus R, herpes-type and paramyxovirus-type viruses, and adenovirus 2-type bodies. In addition to electron microscopic studies on fresh tissues, breast tumor tissues of 157 patients and pleural effusion cells of 36 patients were put into tissue culture. Growth was obtained in 47% of the breast tissue cultures and in 90% of the pleural effusion cell cultures, but no viable cell lines could be established. It was noted, however that B- and C-type virus particles were present in the early passages of four breast tissue culture specimens. Finally, milk specimens were obtained from healthy women and from breast cancer patients; C-type particles were found in the milk of both healthy and cancerous women, B-type particles were found only in specimens of healthy women, and the small virus particles were seen only in the breast cancer patients. Further studies are being performed to clarify the role of the virus particles in tumor cell formation.

- 1693 VIRUS-LIKE PARTICLES IN HUMAN MILK. (E.) Feller, W. F. (Georgetown U. Hosp., Washington, D.C.) and H. C. Chopra. *Cancer* 28(6):1425-1430, 1971.

An electron microscopic study of 59 human milk specimens (16 from women with breast cancer and 43 from normal women) was carried out over a period of seven years. It was found that two types of particles exist in milk. One is a small virus-like particle ranging in size from 20 to 40 mμ, and was discovered in 50% of the milks from breast cancer patients and in 16% of the milks from normal women. In addition to these particles, larger virus-like particles were seen; the larger particles resembled the B- and C-type RNA tumor viruses, and were found in 50% of the milks from women with breast cancer; however, only one normal woman's milk contained the larger particle, and this woman had a positive family history of breast cancer. A detailed review of the literature concerning virus particles in the milk of mammals is presented in the discussion.

- 1694 STUDIES ON VIRUS PARTICLES RESEMBLING ONCOGENIC RNA VIRUSES IN MONKEY BREAST CARCINOMA. (E.) Chopra, H. C. (Nat'l. Cancer Inst., Bethesda, Md.), I. Zelljadt, N. Woodside and M. J. Walling. *Cancer* 28(6):1406-1414, 1971.

A spontaneous neoplasm observed in an 8-year-old female rhesus monkey, *Macaca mulatta*, was biopsied and studied by electron microscopy. It was found that two types of virus particles were present: type A particles, 60 to 95 mμ in diameter, were discovered intracytoplasmically adjacent to the cell surface and were also found in the intercellular spaces; type B particles, 100 to 120 mμ in diameter, were found connected to or lying very near the plasma membranes. After identification these virus particles were isolated successfully from the original tumor and inoculated onto tissue cultures of monkey lung cells, chimpanzee lung cells, mixed human embryo cells, and established human lymphoblastic cells of the line NC-37. All tissue cultures were later found to be infected. So far, however, monkeys inoculated *in vivo* with cell-free virus as well as by infected tissue culture cells have not developed tumors, possibly because of the long latent period of the virus.

- 1695 SEROLOGICAL AND STRUCTURAL PROPERTIES OF MASON-PFIZER MONKEY ISOLATED FROM THE MAMMARY TUMOR OF A RHESUS MONKEY. (E.) Nowinski, R. C. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.), E. Edynak and N. H. Sarkar. *Proc Nat Acad Sci USA* 68(7):1608-1612, 1971.

Mason-Pfizer monkey virus (M-MPV), a virus causing mammary tumors in Rhesus simians, was analyzed serologically and morphologically to determine if similarities to oncornaviruses exist. Virus particles were isolated from an infected mixed culture of monkey embryo and monkey mammary cells. Electron microscopy and sucrose velocity sedimentation was then carried out. It was found that M-MPV has several features similar to those of known oncornaviruses; it has a 60-70S RNA, and it has the enzymes necessary for reverse transcription, and the morphologic features of its replication are essentially the same as those of known oncornaviruses. In addition, actinomycin D was discovered to inhibit viral production. Immunodiffusion studies, however, showed that M-MPV is serologically distinct from the known oncornaviruses, the visna virus, and the three types of simian foamy agent. Preliminary immunologic analysis has failed to reveal the presence of M-MPV structural antigens in human neoplasia.

- 1696 DNA POLYMERASE ACTIVITIES AND NUCLEIC ACID COMPONENTS OF VIRONS ISOLATED FROM A SPONTANEOUS MAMMARY CARCINOMA FROM A RHESUS MONKEY. (E.) Schlom, J. (Columbia U. Coll. Physicians Surg., New York, N. Y.) and S. Spiegelman. *Proc Nat Acad Sci USA* 68(7):1613-1617, 1971.

Mason-Pfizer monkey virus (M-PMV), a spontaneous

mammary RNA tumor virus, was inoculated on cultures of normal human leukocytes, of the cell line NC-37. The cultures were subjected to labeled uridine following infection in order to determine virion density. The radioactive material showed peaks at 1.16 and 1.23 g/ml; the peaks were analyzed by the phenol-pronase method to determine viral nucleic acid characteristics. The M-PMV nucleic acid was made up of high (60-70S) and low (4-6S) molecular weight components. In addition, two minor profiles possessed low sedimentation coefficients; these probably represented internal components of the virion. The high molecular weight virion component banded as RNA on a  $\text{Cs}_2\text{SO}_4$  density gradient. Kinetic studies on the properties of the DNA polymerase activities of the virion showed that three DNA polymerase activities existed, and that these activities responded to either double-stranded DNA or synthetic RNA-DNA hybrid complexes as templates.

- 1697 IMMUNOELECTRON MICROSCOPIC STUDIES OF TYPE C VIRUS PARTICLES IN ESP-1 AND HEK-1-HRLV CELL LINES. (E.) Shigematsu, T. (Anderson Hosp. Tumor Inst., U. Texas, Houston), E. S. Priori, L. Dmochowski and J. R. Wilbur. *Nature* 234(5329):412-414, 1971.

The indirect immunoferritin labelling technique was used to study the morphological and immunological properties of type C virus particles of the ESP-1 cell line, a monolayer cell culture established with cells from pleural effusion of a patient with Burkitt lymphoma. Type C virus particles in the human embryo kidney cell culture infected with the murine Raucher leukemia virus (HEK-1-HRLV) were used for comparison. A thin section of ESP-1 tissue culture was treated with rat anti-MuLV (gs-1) serum followed by ferritin conjugated goat anti-rat IgG. Electron microscopic examination (X90,000) revealed no labelling of type C virus particle. Virus particles in the HEK-1-HRLV cell line were strongly labelled by the same treatment. This test shows that the virus particles are labelled on the viral envelope. It is concluded that the gs-1 antigen of type C virus particles of ESP-1 differs from the gs-1 antigen of the Rauscher murine leukemia type C virus particles. Virus particles in both cell cultures were labelled by ferritin with the rat anti-MuLV (gs-3) serum. The labelling was removed by absorption of the serum with high-speed pellets of either Raucher leukemia virus obtained from spleen of infected (CFW-2) mice or with Gross leukemia virus obtained from spleen of NIH BALB/c mice. These results indicate that the ESP-1 virus particles share an antigenic determinant similar to the group specific, gs-3 (interspecies antigen) of the mammalian leukemia viruses.

- 1698 SPECIFIC INHIBITION OF MAMMALIAN RIBONUCLEIC ACID C-TYPE VIRUS DEOXYRIBONUCLEIC ACID POLYMERASES BY RAT ANTISERA. (E.) Oroszlan, S. (Flow Lab., Inc., Bethesda, Md.), M. Hatanaka, R. V. Gilden and R. J. Huebner. *J Virol* 8(5):816-818, 1971.

Rat antisera, obtained from rats bearing murine leukemia virus induced transplantable tumors, produced specific inhibition of the RNA and DNA dependent DNA polymerase activities of mammalian C-type viruses. This sera did not affect the polymerase activities of murine mammary tumor virus or non-mammalian (Vixen) C-type virus. Sera, obtained from a rat immunized with DNA polymerase, purified by isoelectric focusing, of a feline leukemia virus, inhibited the DNA-dependent DNA polymerase activity of mammalian C-type viruses without any affect on RNA-dependent DNA synthesis. The results indicate the possibility of a method for distinguishing virus specific enzymes in virus transformed or infected cells.

- 1699 SPONTANEOUS FELINE FIBROSARCOMAS: TRANSMISSIBILITY AND ULTRASTRUCTURE OF ASSOCIATED VIRUS-LIKE PARTICLES. (E.) Snyder, S. P. (Comp. Oncol. Lab., U. California, Davis). *J Nat Cancer Inst* 47(5):1079-1085, 1971.

Electron microscopic examination of three of seven tumors from cats with spontaneous fibrosarcoma showed the presence of C-type particles. Seventeen of 20 newborn kittens developed fibrosarcomas when inoculated with cell-free preparations made from each of the three virus-positive and one virus-negative tumors. It was concluded that all four tumors were transmissible. All experimentally induced tumors exhibited C-type particles, 115 mμ in diameter, budding from the plasma membrane. Virus was observed both in cytoplasmic vacuoles and in extracellular spaces.

- 1700 VIRAL INFECTIONS IN MAN ASSOCIATED WITH ACQUIRED IMMUNOLOGICAL DEFICIENCY STATES. (E.) Merigan, T. C. (Stanford U. Sch. Med., Calif.) and D. A. Stevens. *Fed Proc* 30(6):1858-1864, 1971.

A review of several clinical states of immunosuppression associated with viral infection has led to the conclusion that defects in cellular immunity and not defects in immunoglobulin synthesis were correlated with severe viral disease. Among viruses consistently related to immunosuppression were human herpesvirus, vaccinia, two viruses probably belonging to the papova group, and measles virus. Studies on patients with localized or disseminated varicella-zoster infections showed no correlation between the spread of infection and lymphocyte counts, immunoglobulin levels, delayed hypersensitivity to skin antigens and phytohemagglutinin stimulation of lymphocytes. There did appear to be a correlation between dissemination of varicella-zoster and delay in appearance of complement-fixing antibody to the virus and interferon titers. The implications of the above findings were discussed with reference to different therapeutic methods.

- 1701 THE VIROLOGY OF CANCER: PENETRATION OF MATURE VIRUS PARTICLES OF BREAST CANCERS INTO VIRUS-PRODUCING CELLS *IN VIVO*. (Fr.) Thomas, J. A. (Lab. Biol., U. Paris, France), E. Hollande, M. Henry



and C. Vilain. *C R Acad Sci (Paris)*, 273(20):1888-1891, 1971.

An ultrastructural study of the *in vivo* transmission of virus particles of breast cancer in Swiss mouse mammary gland adenocarcinoma (both spontaneous and mammary tumor virus-induced) from cell to cell was made. It was found that penetration of virus particles through the apical and lateral walls of cancer cells is accomplished through the mediation of phagocytic vacuoles surrounding each viral particle. Both immature virus particles which seem to mature in phagocytic vacuoles, as well as extracellular mature particles participate in this penetration; while both mature and immature particles penetrate through the lateral cell wall. It appeared that the walls of phagocyte vacuoles surrounding the mature virus particles were being resorbed by the cytoplasm. Penetration is morphologically identical through both apical and lateral cell walls even though the lining and the physiologic properties of these walls are different. The phenomenon observed corresponds to one modality of horizontal virus transmission. The process *in vivo* is a superinfection because the virus-producing cells are already charged with virus particles. The relationship of this process to vertical genetic transmission is unresolved, as is the meaning of the observed exceptional and paradoxical presence of mature virus particles in cellular nuclei.

1702 INHIBITION OF MITOSIS AND MACROMOLECULAR SYNTHESIS IN RAT EMBRYO CELLS BY KILHAM RAT VIRUS. (E.) Tennant, R. W. (Div. Biol., Oak Ridge Natl. Lab., Tenn.). *J Virol* 8(4):402-408, 1971.

The effects of Kilham rat virus multiplication were studied to determine the mechanisms of virus infection in relation to developmental defects in rats and hamsters. Although cells (rat embryo) were infected with high multiplicities of virus, the efficiency of infection usually did not exceed 30%. Mitosis and DNA synthesis were inhibited within two to ten hours after infection of cells by the virus. Twenty hours after infection, the total RNA synthesis was affected, but only after loss of viable cells became grossly apparent in the cultures did the total protein synthesis decline. Chromosome changes were not seen in the virus-infected cells. Inhibition of the macromolecular system instead of inhibition of uptake of precursors into the cells seemed to account for the effect of Kilham rat virus on DNA synthesis. The effect of virus infection on mitosis was thought to be a consequence of the DNA synthesis inhibition.

1703 DETECTION OF EPSTEIN-BARR VIRAL GENOME IN NONPRODUCTIVE CELLS. (E.) Nonoyama, M. (Sch. Med., U. North Carolina, Chapel Hill) and J. S. Pagano. *Nature New Biol* 233(38):103-106, 1971.

DNA-RNA hybridization techniques for detecting specific regions of chromosomal DNA have been adapted to determine the specific radioactivity of possible Epstein-Barr virus (EBV) DNA in Burkitt lymphoma cells. A

reaction mixture containing Tris, magnesium chloride, dithiothreitol, potassium chloride, bovine serum albumin, GTP, ATP, and CTP,  $^3\text{H}$ -UTP, highly purified *E. coli* DNA-dependent RNA polymerase, and EBV DNA was prepared. The resultant synthesized RNA was analyzed by velocity sedimentation; it was found that radioactivities were distributed over 16S to 4S, with maximum concentrations between 16S and 12S. The RNA, now known as complementary RNA or cRNA, was specificity-tested on three types of cells: the human cell lines HeLa and HEp2 (controls having no EBV genomes); HRIK cells with 700 EBV genomes per cell and HRIK cells with an absence of positive immunofluorescence test; and Raji cells, a Burkitt lymphoma line that does not produce EB virus or antigens but does contain EBV genomes. These Raji cells were studied before and after infection with EBV. After treatment of these three groups with the cRNA mixture it was found that: 1) there is a low background of hybridization in HeLa and HEp2 DNA; 2) the genome number in HRIK cells with a negative IF test drops drastically to 32 EBV genomes per cell; 3) the genome number of Raji cells was shown to increase after infection with EBV. It can be concluded that cRNA preparations such as this are highly specific for EBV-DNA and show EBV-DNA comprising 0.06% to 1.6% of the total DNA of Burkitt lymphoma cells and the established leucocytes tested. It is also suggested that leucocyte cultures *in vitro* may need EBV genomes for continued growth. This possibility is being studied by the authors.

1704 DISTINGUISHING REVERSE TRANSCRIPTASE OF AN RNA TUMOR VIRUS FROM OTHER KNOWN DNA POLYMERASES. (E.) Goodman, N. C. (Coll. Physicians Surg., Columbia U., New York, N.Y.) and S. Spiegelman. *Proc Nat Acad Sci USA* 68(9):2203-2206, 1971.

Three DNA polymerases (viral polymerase from avian myeloblastosis virus (AMV), and two cellular polymerases of *E. coli* and calf thymus) were tested to distinguish the reverse transcriptase of RNA tumor viruses from known normal cellular DNA-instructed DNA polymerases. The comparative responses of the three polymerases to various templates were studied. It was found that only the AMV reverse transcriptase exhibited activity with single-stranded RNA. Oligomer-homopolymer complexes were then tested with the polymerases. The results showed a clear distinction between reverse transcriptase and normal cellular polymerase. Reverse transcriptase was found to prefer initiator-primed synthesis with (dT)<sub>10</sub>·poly(A) as a template, whereas the cellular polymerases gave reactions with (dT)<sub>10</sub>·poly(dA) that were either greater than or equal to those with (dT)<sub>10</sub>·poly(A). Purification of the enzyme preparation must be complete in order for purified single-stranded RNA to serve as a diagnostic device for reverse transcriptase.

1705 BASE COMPOSITION DIFFERENCES BETWEEN AVIAN MYELOBLASTOSIS VIRUS TRANSFER RNA AND TRANSFER RNA ISOLATED FROM HOST CELLS. (E.) Randerath, K. (Massachusetts Gen. Hosp., Boston), L. J. Rosenthal

and P. C. Zamecnik. *Proc Nat Acad Sci USA* 68(12): 3233-3237, 1971.

Major and minor base constitution data for normal chicken liver, myeloblast, and avian myeloblastosis virus (AMV) 4S RNA was collected by means of a novel isotope derivative method. Stoichiometric incorporation of tritium into periodate-oxidized enzymatic digests of RNA was induced, followed by chromatographic resolution of the labelled digests into individual radioactive nucleoside derivatives; liquid-scintillation counting was used to assay the RNA. Substantial base composition differences exist between AMV 4S RNA and host-cell 4S RNA, but these differences were nonrandom, since: 1) the concentrations of all methylated guanines were elevated in the tumor virus RNA; 2) the concentration of inosine was depressed in virus RNA; and 3) the concentrations of all modified pyrimidines were lower in the tumor virus RNA. Once infection had occurred, the differences between normal cells and tumor cells were found to be small or undetectable. The amount of methylated bases in viral RNA was found to be similar to that in normal host cells; and viral 4S RNA, therefore, appears to be derived from a precursor population of host-cell 4S RNA. Three possibilities to explain the mechanism responsible for such differences and similarities were given: 1) the virion may contain specific methylases or demethylases that modify host-cell t RNA; 2) the viral RNA genome may code for new individual tRNAs by its own reverse transcriptase and the host-cell RNA polymerase; or 3) there may be a selective screening of host-cell tRNAs as the virion pinches off from the host cell.

1706 PRIMER REQUIREMENT AND TEMPLATE SPECIFICITY OF THE DNA POLYMERASE OF RNA TUMOR VIRUSES. (E.) Baltimore, D. (Massachusetts Inst. Tech., Cambridge) and D. Smoler. *Proc Nat Acad Sci USA* 68(7):1507-1511, 1971.

Known DNA polymerases apparently are unable to initiate deoxyribonucleotide polymerization *de novo* on a single stranded template but require a primer containing a free 3'-OH. A series of experiments with poly(A) and oligo(dT) have shown this to be true and have provided an assay method for the template specificity of the DNA polymerases of avian myeloblastoma virus (AMV). Incubation of virions of AMV with labeled deoxynucleoside triphosphates led to little or no incorporation. The addition of poly(A) alone slightly stimulated incorporation, while addition of either poly(dT) or poly(dT)<sub>14</sub> with poly(A) caused a marked stimulation. Maximal rates of incorporation were achieved by adding equimolar concentrations of the triphosphate molecules, proving that the number of free 3'-OH ends is the critical factor. Measurement of yields of synthesis showed that a poly(A)·poly(dT) duplex was the final product. Studies on the reactions of Moloney leukemia virus (MLV) and AMV to homoribopolymers indicated that specificities were different for both viruses. These experiments demonstrate: 1) that both a template and a primer are necessary for stimulation of the AMV DNA polymerase; 2) that the

primer must be either a polydeoxyribonucleotide or preferably a polyribonucleotide; and, 3) that DNA-dependent DNA polymerases and RNA-dependent RNA polymerases are distinguishable.

1707 INDUCTION OF AVIAN TUMOR VIRUSES IN NORMAL CELLS BY PHYSICAL AND CHEMICAL CARCINOGENS. (E.) Weiss, R. A. (U. Washington Sch. Med., Seattle,), K. R. Friis, E. Katz and P. K. Vogt. *Virology* 46(3):920-938, 1971.

Chick embryo cells of Line 7, Reaseheath C line (gs<sup>-</sup>) and I line, White Leghorn (gs<sup>-</sup>), and red jungle fowl were tested for release of avian tumor virus particles after treatment with ionizing radiations and chemical mutagens and carcinogens. It was found that virus particles could be educed from both gs<sup>+</sup> and gs<sup>-</sup> cell lines, indicating that the viral genome for leukosis virus was present in all chicken cells. Therefore, the chromosomal locus which controls the presence of natural gs antigen does not represent the viral genome itself but regulates its expression in normal cells. Characterization of induced leukosis virus (ILV) particles released from affected cells showed that these viruses are members of the group known as avian RNA tumor viruses. The virus particles cosedimented with known avian tumor viruses and possessed the RNA-dependent DNA polymerase, the polypeptides, as well as the 70S RNA typical of avian tumor viruses. They acted as helper viruses for RSV by phenotypic mixing. Generally, they belonged to the avian tumor virus subgroup E, as determined by host-range, interference, and antigenicity.

1708 CHROMATOGRAPHIC SEPARATION AND ANTIGENIC ANALYSIS OF PROTEINS OF THE ONCORNA-VIRUSES: I. AVIAN LEUKEMIA-SARCOMA VIRUSES. (E.) Fleissner, E. (Sloan-Kettering Inst., New York, N.Y.). *J Virol* 8(5):778-785, 1971.

Seven major protein species are clearly resolved by gel filtration of avian tumor virus proteins in 6M guanidine hydrochloride. Following removal of the denaturing solvent, the good yield of antigenic activity of these proteins permitted a correlation of specific polypeptides with the principal antigens of the virion. Two of the proteins situated on the viral membrane had molecular weights of 70,000 and 32,000 and contained carbohydrate. Four proteins enclosed within the viral membrane have molecular weights (in guanidine) of 27,000, 19,000, 15,000 and 12,000 and have different group-specific (gs) antigens. A protein with a molecular weight of 10,000 was found which had not been previously described. It showed a mobility identical to that of one gs protein when run on polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate. It was not detectable with antisera. Five proteins were lacking carbohydrate, three were present in the virion in a molecular ratio of 2:2:1. The other two were present in almost equal amounts and were rich in arginine and lysine.



- 1709 SPECIFIC RNA METHYLASE ASSOCIATED WITH AVIAN MYELOBLASTOSIS VIRUS. (E.) Gantt, R. R. (Nat'l. Cancer Inst., Bethesda, Md.), K. J. Stromberg and F. Montes De Oca. *Nature* 234(5323):35-37, 1971.

A specific RNA methylase has been found associated with avian myeloblastosis virus (AMV). This enzyme transfers a methyl group from S-adenosylmethionine to RNA guanine to produce N<sup>2</sup>-methylguanine. The reaction was found to depend on the presence of tRNA and on the addition of a nonionic surfactant to the mixture. Enzyme activity was stable after freezing and thawing but was destroyed by heating for three minutes at 100° C in standard assay buffer. No activity was observed using *E. coli* DNA as substrate. Only one eighth the activity was seen when yeast tRNA was substituted.

- 1710 STRUCTURAL PROTEINS OF RAUSCHER LEUKEMIA VIRUS AND HARVEY SARCOMA VIRUS. (E.) Moroni, C. (Salk Inst. Biol. Stud., San Diego, Calif.). *Virology* 47(1):1-7, 1972.

JLS-V5 cells secreting Rauscher leukemia virus (RLV) particles were passaged in pulse-labelled tissue culture until a sufficient quantity of radioactive virus could be purified from the supernatant media. After purification by equilibrium density gradient centrifugation, proteins of the RLV particles were separated by SDS-polyacrylamide gel electrophoresis. Five peaks were eluted by this method. Further biochemical studies on each peak indicated that peak I of molecular weight 15,000 contained a relatively high ratio of arginine and other amino acids, while peak V and minor components of peaks I and IV contained glycoproteins. Another protein, corresponding to peak I--the main peak that was eluted, reacted significantly with group-specific (gs) antiserum thus indicating the presence of internal viral components. Pulse-chase experiments showed that peaks IV and V had different kinetics from the other components. These preliminary results indicate that the viral glycoproteins which are presumably assembled in the virus envelope at the cell membrane are regulated in a manner different from other components. Examination of Harvey sarcoma virus (HSV) protein has yielded similar electrophoretic results.

- 1711 QUANTITATIVE STUDIES OF NATURALLY OCCURRING MURINE LEUKEMIA VIRUS INFECTION OF AKR MICE. (E.) Rowe, W. P. (Nat'l. Inst. Hlth., Bethesda, Md.), and T. Pincus. *J Exp Med* 135(2):429-436, 1972.

Measurements of infectious murine leukemia virus (MLV) in tissues of mice of the strain AKR were performed; the quantity of MLV infection was described as a function of age and presence or absence of leukemia. MLV infectivity tests were done in secondary cultures of NIH strain Swiss mouse embryo; NIH Swiss embryos were cultured and inoculated with extracts of various tissues of AKR mice.

MLV was not found in 16- or 17-day AKR embryos, was present in trace amounts in two of six carcass extracts of 18- to 19-day embryos, and was subsequently found with increasing consistency and gradually increasing titer as compared to nonleukemic mice of the same age. While virus was found in considerable amounts in all tissues, there was a 30- to 100-fold difference between organs in quantity of detected virus, with highest virus titers being found in bone, including the tail and the cortex and marrow of the femur, and in the uterus and spleen. Virus titers in normal thymus were relatively low, but increased significantly with the development of thymic lymphoma. It was striking that high virus titers were found in the uterus, a site in which spontaneous tumors rarely develop.

- 1712 TUMOR INDUCTION IN HAMSTER BY PARA(3cT)-ADENOVIRUS 7 MUTANT: MORPHOLOGY AND ANTIGENIC PROFILES OF NEOPLASTIC CELLS. (E.) Pauluzzi, S. (Inst. Infec. Dis., Perugia U., Italy) and R. Ribacchi. *Int J Cancer* 8:523-530, 1971.

A report on the oncogenicity of the PARA (3cT)-adenovirus 7 (Ad 7) mutant, as well as a description of the morphology of induced tumors and the antigenic profiles of some derivative cell lines, is presented. The plaque-purified PARA (3cT)-Ad 7 mutant was used following six additional passages in African green monkey kidney cells, with the adenovirus titer being determined by plaque formation in hamster embryo kidney cells. Three groups of newborn, random bred Syrian hamsters were injected s.c. with the virus preparations, either PARA (3cT)-Ad 7, PARA-Ad 7, or Ad 7 alone; 13 of 25 hamsters injected i.p. with PARA (3cT)-Ad 7 and all animals treated with Ad 7 also were injected i.p. with anti-hamster lymphocyte horse (ALH) serum at one, five, and 12 days of age, receiving 0.1, 0.2, and 0.3 ml, resp. Weekly tumor examinations were made, with excision of tumors greater than 20 mm in diameter. The incidence of tumor development in hamsters inoculated with PARA (3cT)-Ad 7, PARA-Ad 7, and Ad 7 was 20, 13.3, and 16.6%, resp., with a mean latency period of 126, 100, and 323 days, resp. "Early" (in two- to four-month-old animals) tumors induced by all virus preparations were characterized by features of typical undifferentiated adenovirus-type neoplasms. "Late" (in five- to seven-month-old animals) tumors induced by PARA (3cT)-Ad 7 were found to be multifocal sarcomas having wide morphologic differences in the same growth; all "late" tumors had a well-developed reticulin network. Seven cell lines derived from six tumors showed three different cytomorphologic types: Type A had small cells with a large nucleus and scanty cytoplasm; Type B had larger elongated cells, a large round nucleus, abundant cytoplasm, and a number of giant cells; Type C had fibroblast-like cells similar to Type B cells except that they sometimes contained strange, ribbon-like perinuclear elements. Two cell lines from "early" PARA (3cT)-Ad 7 tumors contained SV40 antigen in addition to adenovirus T antigen. It was shown that the PARA (3cT)-Ad 7 mutant still retained the oncogenic capability of PARA-Ad 7 *in vivo*.

- 1713 MECHANISM OF THE ARGININE REQUIREMENT FOR ADENOVIRUS SYNTHESIS: I. SYNTHESIS OF STRUCTURAL PROTEINS. (E.) Everitt, E. (Wallenberg Lab., Uppsala U., Sweden), B. Sundquist and L. Philipson. *J Virology* 8(5):742-753, 1971.

This study attempts to quantitate the levels of arginine needed for synthesis of virus and structural proteins. The synthesis of structural proteins under normal one-step growth conditions is described. The logarithmic synthesis of the three main structural units, hexon, penton base, and fiber, was studied at normal arginine concentration in adenovirus 2-infected KB cell monolayers and spinner cultures. The major core protein AAP was synthesized in excess one hour after the penton base. During the linear increase in structural proteins at 15 to 30 hours post-infection, the hexon and fiber antigen were present in a final molar ratio of 0.5:1. The level of arginine in the adenovirus 2-infected cultures was varied in the second part of the study: the arginine-sensitive step occurred as early as 15 hours postinfection. Total arginine depletion was found to reduce virus yield by more than 1,000-fold, although structural proteins accumulated in excess. Furthermore, the molar ratio of the fiber antigen to hexon varied from three to six. When the arginine depletion was reversed, a four- to five-hour lag period was observed before the increase in virus particle growth, with hexon synthesis taking place at the highest rate and primary synthesis of virion polypeptides also occurring. These results indicate that the majority of the proteins maturing into virus particles at arginine reversion are formed after addition of high concentrations of arginine, and that the considerable excess pool of structural units present at arginine depletion is not available for virus synthesis.

- 1714 THE MECHANISM OF VIRAL CARCINOGENESIS BY DNA MAMMALIAN VIRUSES: RNA TRANSCRIPTS CONTAINING VIRAL AND HIGHLY REITERATED CELLULAR BASE SEQUENCES IN ADENOVIRUS-TRANSFORMED CELLS. (E.) Tsuei, D. (St. Louis U. Sch. Med., Mo.), K. Fujinaga and M. Green. *Proc Nat Acad Sci USA* 69(2):427-430, 1972.

Virus-specific RNA was isolated from adenovirus 2-transformed rat embryo cells and from adenovirus 7-induced hamster tumor cells by repeated hybridizations with and elutions from purified homologous viral DNA. Virus-specific <sup>3</sup>H-RNA from adenovirus 2- and adenovirus 7-transformed cells hybridized not only with viral DNA (24-40% and 36-50%, resp.) but also with DNA purified from untransformed host cells (12-25% and 16-19%, resp.). <sup>3</sup>H-RNA bound insignificantly to empty filters or to filters containing *E. coli* DNA. Virus-specific <sup>3</sup>H-RNA derived from KB cells productively infected with adenovirus 2 or 7 hybridized to homologous viral DNA (26-42% efficiency) but not to DNA of untransformed KB, rat, hamster, or *E. coli* cells. It is concluded that RNA molecules containing covalently-linked viral and cellular sequences are transcribed in cells transformed by human adenoviruses and that viral DNA is integrated adjacent to highly reiterated cellular DNA sequences.

- 1715 ON THE FATE OF ADENOVIRUS DNA IN KB CELLS. (E.) Sussenbach, J. S. (Lab. Physiol. Chem. St. U. Utrecht, Netherlands). *Virology* 46(3): 969-972, 1971.

This study was undertaken to examine the mechanism of adenovirus DNA replication and to determine the fate of the parental DNA molecules. Adenovirus type 5 (Ad5) and type 12 (Ad12) were used. Degradation of viral DNA in the nuclei of KB cells infected with <sup>3</sup>H-labeled Ad5 or Ad12 was studied. It was shown that Ad12 DNA was almost completely converted from 30S to 20S fragments; in Ad5, however, no degradation was detected. Using mitomycin C to block residual cellular DNA synthesis, KB cells were infected with nonlabeled Ad5 and Ad12. The results demonstrated that the newly synthesized viral DNA was not of cellular origin or in single-stranded form. A pulse-chase experiment done to determine the origin of the 20S molecules of the new Ad12 DNA showed that the amount of labeled DNA did not increase, and that the distribution of labeled 30S and 20S molecules remained unchanged. It was concluded that 20S molecules are probably not formed by degradation of 30S molecules.

- 1716 PHYSICO-CHEMICAL PROPERTIES OF THE DNA OF HERPES VIRUSES. (E.) Graham, B. J. (Baylor Coll. Med., Houston, Texas), H. Ludwig, D. L. Bronson, M. Benyesh-Melnick and N. Biswal. *Biochim Biophys Acta* 259(1):13-23, 1972.

DNA isolated from strains XIII and KOS of herpes simplex virus (HSV) type 1, strains SA and 307 of HSV type 2, infectious bovine rhinotracheitis virus (IBRV) and pseudorabies virus (PRV) were characterized by their buoyant densities in CsCl, base composition, thermal denaturation patterns, and sedimentation coefficients in neutral tris-saline buffer. HSV-1 showed a major DNA peak at a buoyant density of 1.725 g. per cm<sup>3</sup>. HSV-2, PRV and IBRV DNAs banded at 1.727, 1.731 and 1.730 g. per cm<sup>3</sup> resp. Sedimentation coefficients for HSV-1, HSV-2, and two components of PRV DNA were 56±4S, 56±4.5S, and 26.4 ± 0.72S and 30.6 ± 1.9S resp. These corresponded to molecular weight of 87.7 (±14) × 10<sup>6</sup> for HSV-1 DNA, 87.7 (±15) × 10<sup>6</sup> for HSV-2 DNA and 16.1 × 10<sup>6</sup> and 22.3 × 10<sup>6</sup> resp. for the two PRV DNA components. The midpoints of thermal denaturation for DNAs of HSV-1, HSV-2, PRV and IBRV were 82.6 C, 82.7 C, 86.6 C and 85.6 C resp. (A+T)/(G+C) ratios for HSV-1, HSV-2 and PRV DNA were 0.43, 0.39 and 0.30.

- 1717 EARLY FUNCTIONS OF THE GENOME OF HERPES-VIRUS: INHIBITION OF THE FORMATION OF CELL-SPECIFIC POLYSOMES. (E.) Ben-Porat, T. (Albert Einstein Med. Ctr., Philadelphia, Pa.), T. Rakusanova and A. S. Kaplan. *Virology* 46(3):890-899, 1971.

Polysomes present in rabbit kidney cells infected with the herpes simplex virus, pseudorabies, were isolated by density gradient centrifugation into two bands: a large-polysome band (> 230S) and a small-polysome band (230-120S). RNA was extracted from these bands, and biochemical studies were run



to determine the mechanism of inhibition during the synthesis of cell-specific protein. Annealing techniques indicated that 65% of the virus-specific RNA was located in the larger polysomes. Radioactive labeling revealed that large polysomes had a lower lysine:leucine ratio than did the small polysomes. Studies conducted on intact infected cells exposed to actinomycin and cycloheximide showed that actinomycin could prevent the decrease in the incorporation of lysine into proteins that occurred after infection of the cells with pseudorabies virus. Inhibition of cell-specific protein synthesis occurred only if the RNA synthesis was allowed to proceed in the infected cells. In the absence of RNA synthesis, the gradual inhibition of cell-specific protein synthesis that occurred normally in infected cells was arrested. Both cell-specific and virus-specific polysomes were present in the cycloheximide-treated, infected cells, but these polysomes were not functional until the cycloheximide was withdrawn. These results imply that inhibition of cell-specific protein is one of the immediate early functions of the viral genome.

1718 SEROEPIDEMIOLOGIC STUDIES OF HERPESVIRUS TYPE 2 AND CARCINOMA OF THE CERVIX.

1. CASE-CONTROL MATCHING. (E.) Adam, E. (Baylor Coll. Med., Houston, Texas), H. Levy, W. E. Rawls and J. L. Melnick. *J Nat Cancer Inst* 47(5):941-951, 1971.

This report deals primarily with methods of case-control matching and the influence of matching on data related to frequency of antibodies to herpesvirus type 2 among women with cervical cancer and control women. Two geographically distant areas (A and B) with a high prevalence of cervical carcinoma were selected for the study. Normal women in area B were prematched with cancer patients in terms of age, race and socioeconomic level, while normals in area A were chosen without attempting to match them for characteristics of area A cancer patients. A number of demographic features were found to be related to the incidence of squamous cell carcinoma of the cervix, including: present age of the individual; socioeconomic level; and such sexual and reproduction-associated factors as age at first intercourse, age at first marriage, age at first pregnancy, number of live births, number of marriages, and number of sex partners. When prematching was used, no significant differences in the occurrence of antibodies to herpesvirus type 2 were found between cancer patients and the control women. It was concluded that although the mean values for occurrence of antibody in both areas were similar, the matching procedure using a weighted sum of the differences between each case and each control in the factors used for matching facilitated the selection of a control group.

1719 TYPE-SPECIFIC SURFACE ANTIGENS OF CELLS INFECTED WITH HERPES SIMPLEX VIRUS (1 AND 2). (E.) Nahmias, A. J. (Emory U. Sch. Med., Atlanta, Ga.), I. DelBuono, K. E. Schneiweis, D. S. Gordon and D. Thies. *Proc Soc Exp Biol Med* 138(1):21-27, 1971.

Use of direct and indirect immunofluorescent techniques in the study of type-specific surface antigens of cells infected with herpes simplex virus (HSV) 1 and 2 are described. The fluorescein-conjugated anti-HSV sera specific for HSV-infected cells containing type-specific membrane antigens for each of the two HSV types were prepared by sorption procedures using antisera with HSV-infected-cells with heterologous sera or with heterologous virus-infected cells. By means of the indirect fluorescent antibody technique, HSV IgA antibodies were seen in genital secretions of women with recent HSV genital infections, as were HSV antibodies to the IgG, IgA or IgM serum fractions. Results of these experiments supported the working formula for antigens of HSV: type 1 HSV = AC and type 2 HSV = BC (where A, B or C may be more than one antigen). The HSV-infected cells with type-specific membrane antigens provided a more specific typing method for type 1 and type 2 antibodies.

1720 SUPPRESSED SYNTHESIS OF VIRAL DNA, PROTEIN, AND MATURE VIRIONS DURING REPLICATION OF CANINE HERPESVIRUS AT ELEVATED TEMPERATURE. (E.) Lust, G. (Vet. Res. Inst., Cornell U., Ithaca, N.Y.) and L. E. Carmichael. *J Infect Dis* 124(6):572-580, 1971.

Canine herpes virus (CHV) development and factors associated with biosynthesis of viral protein and DNA were studied in cultures of secondary dog-kidney cells (DKC) at 36.5° and 40°C. Although growth of CHV in DKC was normal at 36.5°C, yields of infectious virus decreased 10<sup>3</sup>- to 10<sup>4</sup>-fold at 40°C. CF antigen titers, as well as DNA synthesis, were reduced two-fold at 40°C. Inhibition of viral DNA synthesis at 40°C by cytosine arabinoside during the first two hr of infection inhibited viral protein synthesis and prevented cytopathologic effects and formation of infectious virus. Uptake of labelled precursor into macromolecules indicated that RNA and protein synthesis in uninfected cells were not affected by raising the temperature from 36.5 to 40°C although DNA synthesis was decreased slightly. Autoradiographic analysis of viral DNA synthesis showed no difference between 36.5° and 40°C six hr after infection, but by 12 hr postinfection there were fewer grains over cells at 40°C. Infected cells incubated at 36°C for up to eight hr and shifted to 40°C made infectious virus as if the whole growth cycle took place at 40°C. When infected cells were kept at 40°C for eight hr and then shifted to 36°C, titers of infectious virus were as if the whole growth cycle had occurred at 36°C. These results indicate that failure to produce infectious CHV at 40°C occurred late in the replication cycle due to a combination of decreased viral DNA and protein synthesis, in conjunction with deranged maturation of virions.

1721 STUDIES ON THE RELATEDNESS OF HERPES VIRUSES THROUGH DNA - RNA HYBRIDIZATION. (E.) Bronson, D. L. (Baylor Coll. Med., Houston, Texas), B. J. Graham, H. Ludwig, M. Benyesh-Melnick and N. Biswal. *Biochim Biophys Acta* 259(1):24-34, 1972.

Saturation and competition hybridization studies were conducted to determine the degree of homology between strains XIII, KOS and DOR of herpes simplex virus (HSV) type 1, strains SA and 307 of HSV type 2, pseudorabies virus (PRV) and infectious bovine rhinotracheitis virus (IBRV). A high degree of homology was observed between XIII, KOS and DOR HSV-1 strains, as well as between SA and 307 HSV-2 strains. No significant homology existed between PRV and IBRV or between any of the HSV strains and either PRV or IBRV. Partial homology (14% to 40%) was seen between HSV-1 and HSV-2.

1722 FURTHER STUDIES ON THE MODE OF TRANSMISSION OF HERPES-LIKE VIRUS IN GUINEA PIGS.

(E.) Lam, K. M. (Yale U. Sch. Med., New Haven, Conn.) and G. D. Hsiung. *Proc Soc Exp Biol Med* 138(2):422-426, 1971.

Studies were made to determine if a herpes-like virus (HLV) could be transmitted by intranasal or oral inoculation in Hartley guinea pigs. The effects of age on HLV growth in infected animals and the frequency of HLV infection in their offspring were also investigated. Seven guinea pigs were inoculated orally with HLV and 12 were inoculated intranasally. In a total of nine experiments, the ability to detect HLV in the blood depended on the amount of virus inoculated. Virus was ultimately detected in four of seven orally inoculated animals and in ten of 12 intranasally inoculated animals. Two of eight guinea pigs were susceptible to contact infection when placed either in the same cage with or in cages adjacent to infected animals. None of the offspring of animals intracerebrally inoculated had detectable HLV blood titers. Of 60 offspring from intraperitoneally infected parents, only six showed virus infection when tested at less than two months old. Positive blood titers were seen in 17 of 26 two- to six-months-old offspring of intraperitoneally infected animals. All of four animals intracardially inoculated with HLV showed virus in blood samples by 16 days postinoculation.

1723 HERPESVIRUS TYPE 2 ISOLATED FROM CERVICAL TUMOR CELLS GROWN IN TISSUE CULTURE. (E.)

Aurelian, L. (Johns Hopkins Sch. Med., Baltimore, Md.), J. D. Strandberg, L. V. Melendez and L. A. Johnson. *Science* 174(4010):704-707, 1971.

Herpesvirus type 2 (HSV-2) was detected in a degenerating culture of cervical carcinoma cells after ten transfers (six months) *in vitro*. Infection of HEP-2 cells with an extract made by freezing and thawing a cell suspension produced cytopathologic effects (CPE). Infection using an extract from control S332G cells produced no CPE. The virus was identified in S332G-infected HEP-2 cells on the basis of characteristic cellular ultrastructural changes. Complete or incomplete virus particles were not seen in viable S332G cells themselves. Immunofluorescence studies were positive at greater dilutions for rabbit antiserum to HSV-2 than for antiserum to HSV-1. Neutralization tests also indicated the presence of HSV-2.

1724 TEMPERATURE-SENSITIVE MUTANTS OF HERPES SIMPLEX VIRUS TYPE 2. (E.) Timbury,

M. C. (Inst. Virol U. Glasgow, Scotland). *J Gen Virol* 13(2):373-376, 1971.

This report describes the isolation and preliminary classification of temperature-sensitive mutants of herpes simplex virus type 2. Control virus of the strain HSG 52 was grown in BHK 21 clone 13 cells. Temperature-sensitive mutants were then obtained by treatment of the HSG 52 virus particles with 5-bromo-deoxyuridine. Cells from all mutagenized cultures were cloned repeatedly until 32 stable temperature-sensitive mutants from a preliminary experiment were obtained; in addition, one other temperature-sensitive mutant from a preliminary experiment was used. Initial tests on the mutants for complementation were unsuccessful. However, when the infectious center assay was tried, it was found that the mutants complemented each other in all combinations, thus proving that they belonged to ten different complementation groups. Since the molecular weight of herpes simplex DNA is  $100 \times 10^6$ , the virus theoretically can code for 100 average-sized proteins. The ten complementing groups are, therefore, only a fraction of the total number of expected cistrons of the virus genome with the remaining 23 mutants still being tested.

1725 INHIBITION OF OCULAR HERPES SIMPLEX INFECTION IN RABBITS BY EXTRACTS OF BURKITT'S LYMPHOMA CELL CULTURES. (E.) Albert, D. M. (Yale U. Sch. Med., New Haven, Conn.) and A. S. Rabson. *Proc Soc Exp Biol Med* 138(1):108-111, 1971.

Studies were made to determine whether an inhibitor of herpes simplex virus (HSV) could inhibit progression of herpes simplex keratitis in the rabbit cornea *in vivo*; the inhibitor of HSV was found in extracts of cells derived from a Burkitt's lymphoma. Burkitt's lymphoma extract was instilled topically into eyes infected with HSV. One rabbit in each of ten pairs was infected with HSV and treated with Burkitt's lymphoma extract; the other member of the pair was infected with HSV but was not treated with extract. It was found that the Burkitt's lymphoma extract cured or suppressed the progression of ocular herpetic keratitis. Histopathologic studies of the eyes of animals treated with Burkitt's lymphoma extract showed generally less severe or absent keratitis, uveitis, retinitis and papillitis as compared to animals infected with HSV but not treated with extract.

1726 CHARACTERISTICS OF THE STRUCTURAL COMPONENTS OF THE MOUSE MAMMARY TUMOR VIRUS: II. VIRAL PROTEINS AND ANTIGENS. (E.) Nowinski, R. C. (Sloan-Kettering Inst., New York, N.Y.), N. H. Sarkar, L. J. Old, D. H. Moore, D. I. Scheer and J. Hilgers.

*Virology* 46(1):21-38, 1971.

An immunological analysis of the mouse mammary tumor virus (MTV) structural proteins is reported; several separate but related series of experiments were in-



involved. MTV was purified from the milk of congenitally MTV-infected C3H/An and C3H/HeJ mice and treated with Tween 80 ether to bring about the release of subviral components. Soluble virus proteins were chromatographed on Sephadex G-200 and used as antisera to immunize rats; five serologically distinct viral antigens were identified by these antisera (MTV-s1, s2, s3, s4 and s5). Antigens s1 and s2 were group-specific, and were the antigens of the viral nucleoid. The MTV-s3 antigen was a structural protein of the viral membrane. Antisera prepared against MTV or isolated MTV proteins did not react with murine leukemia virus antigens; nor did antisera against the latter virus react with MTV antigens. Polyacrilamide gel electrophoresis of SDS-disrupted MTV showed five major proteins of the virion (p1-p5); molecular weights of these five proteins were estimated as: p1, 90,000; p2, 70,000; p3, 52,000; p4, 33,000; and p5, 23,000. The p3 protein was the major protein of the virus; p3 was found in the nucleoid and carried the s1 antigen. Antisera against MTV proteins were used in immunofluorescence tests to determine the intracellular deposition of viral structural components. All immunofluorescence reactions with MTV antisera were cytoplasmic; no nuclear fluorescence was seen. Rabbit anti-MTV serum was used in immunodiffusion tests to detect MTV antigens in extracts of a wide variety of neoplastic tissues. Results indicated that MTV infection was restricted to three neoplastic tissues: mammary tumors of MTV-infected mice; ML+ leukemias; and a Leydig cell tumor of MTV-infected mice. Rat antisera against isolated MTV proteins were used in immunodiffusion tests to identify individual viral components in virus-infected cells. All extracts of mammary tumors and ML+ leukemias were positive for the s1 and s2 antigens. Electron microscopic examination of three ML+ leukemias and the Leydig cell tumor revealed large intracytoplasmic inclusions of A-type particles, but revealed no budding virions.

- 1727 HISTOCOMPATIBILITY GENES AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS (MTV) IN MICE. (E.) Mühlbock, O. (Netherlands Cancer Inst., Amsterdam), and A. Dux. *Transplantation Proc* 3(3):1247-1250, 1971.

Mammary tumor virus (MTV) has three different variants. Two of these variants have been investigated in this work: C3H-MTV, which is transmitted by the mothers' milk, and GR-MTV, transmitted at conception by either the sperm or the ovum. Congenic resistant (CR) strains and normal strains of the C57BL/10 mice were subjected to four separate experiments. In the first, newborn mice were given C3H-MTV by way of the milk. It was found that the CR-strains in which the H-2<sup>b</sup> allele of the B10-strain mice is replaced by the alleles 2<sup>a</sup>, 2<sup>d</sup>, 2<sup>f</sup>, 2<sup>k</sup>, and 2<sup>m</sup> have a significantly higher incidence of tumor formation than both the B-10 strain and the CR-strains with H-2<sup>b</sup> allele but with different weak histocompatibility loci 1<sup>a</sup>, 1<sup>b</sup>, 3<sup>b</sup>, 8<sup>b</sup> and 9<sup>b</sup>. In the second experiment 2-month-old females of the CR-strain were injected i.p. with cell-free mammary tumor extract. Mammary tumor incidence was found to be higher in the females with the H-2 alleles 2<sup>a</sup>, 2<sup>f</sup>, and 2<sup>m</sup> than in females with the H-2<sup>b</sup> allele.

Replacing the different alleles at the weak histocompatibility loci had no influence. In the third experiment, GR-MTV was transmitted by males or females at conception to hybrid F<sub>1</sub> mice. Hybrids of all CR strains had a high percentage of tumors, regardless of histocompatibility loci. Lastly, GR-MTV was given to newborn females through the lactation process. Females carrying the H-2<sup>b</sup> allele were found to be slightly more susceptible to tumors than those carrying other alleles. The influence of the H-2 locus on the susceptibility to MTV is thus only apparent with C3H-MTV.

- 1728 INCREASE AND MODIFICATION OF THE CARCINOGENIC POWER OF MAMMARY TUMOR VIRUS AFTER ETHYLENE OXIDE TREATMENT: DISTRIBUTION OF VIRAL PARTICLES. (Fr.) Thomas, J. A. (Lab. Biol., U. Paris, France), C. Lambre and M. Henry. *C R Acad Sci (Paris)* 273(18): 1650-1653, 1971.

An attempt was made to immunize mice against the mammary tumor virus (MTV) following its presumed attenuation by ethylene oxide. Mammary adenocarcinoma inoculum (T III strain) treated with 0.5% ethylene oxide and 10% glycerol was administered i.p. to young male and female mice (Swiss, CD1 and LAB) in three injections of 0.5 ml each (second and third injections after 13 and 29 days, resp.). Control animals received the same inoculum without ethylene oxide. In 37.5% of the 80 Swiss mice, tumors were observed between the 14th and 550th days; the corresponding percentage for the control group was 11.8%. Mammary adenocarcinomas were observed in 22 cases, with typical metastases in nine cases. Pulmonary metastases were relatively large, and cancer dissemination was very frequent in the thorax and abdomen. Regression of the primary mammary cancer with small residual adenocarcinoma was observed in one case. Adenocarcinomatous metastases without anatomically ascertained mammary adenocarcinoma were found in five cases. Virologic investigations of primary mammary carcinomas with and without metastasis revealed the presence of both A and B forms of MTV particles; the B form was predominant in histologically typical metastases, particularly in the lung. Forms A and B were detected in adenocarcinomatous metastases with atypical mammary structure. MTV particles were found in anaplastic liver and spleen carcinomas and in mesenteric metastases. Leukemic C particles were found in the thymus of a mouse bearing anaplastic carcinoma of the liver and spleen. Other particles, not yet identified, also occurred in a spleen carcinoma. Both A and B forms of MTV were present in the control group. Treatment of the MTV with ethylene oxide seems to have enhanced rather than diminished its carcinogenicity.

- 1729 CLONAL ISOLATION OF MURINE SARCOMA VIRUS (MSV): CHARACTERIZATION OF VIRUS PRODUCED FROM TRANSFORMED CELLS. (E.) Somers, K. (Baylor Coll. Med., Houston, Texas) and S. Kit. *Virology* 46(3):774-785, 1971.

Normal rat kidney (NRK) cells were exposed to murine

sarcoma virus (MSV); the cells were cloned by the agar overlay method when infection was complete. Six MSV-transformed NRK clones were then isolated and two of them, NRK(MSV-1) and NRK(MSV-6), were subjected to titration kinetics studies, radioactive labelling analyses, infectivity experiments, and virus particle analyses. Both transformed clones released particles that could be banded in sucrose at 1.15 g/cm<sup>3</sup> and contained 70 S RNA. However, NRK(MSV-1) cells could release virus particles capable of transforming other normal NRK cells but these secondarily transformed cells failed to produce new virus particles unless further treated with Moloney leukemia virus (MoLV), whereupon the secondarily infected cells produced infectious MSV with the host range characteristic of the MoLV pseudotype. On the other hand, NRK(MSV-6) cells released a particle for which no infectivity has yet been demonstrated. Furthermore, infectious virus could not be rescued from the NRK(MSV-6) cells even when superinfection with either MoLV or Murine erythroblastosis virus (MEV) was carried out. It seems likely, therefore, that MSV defectiveness is relative and depends upon the host cell employed in the assay procedure.

1730 3-CYCLIC AMINE DERIVATIVES OF RIFAMYCIN: STRONG INHIBITORS OF THE DNA POLYMERASE ACTIVITY OF RNA TUMOR VIRUSES. (E.) Green, M. (St. Louis U. Sch. Med., Mo.), J. Bragdon and A. Rankin. *Proc Nat Acad Sci USA* 69(5):1294-1298, 1972.

Thirty-seven 3-amine derivatives of rifamycin-SV dissolved at a concentration of 5 mg/ml in dimethylsulfoxide (Me<sub>2</sub>SO) or in a 1:1 mixture of H<sub>2</sub>O Me<sub>2</sub>SO that was 12 mM in sodium ascorbate and 30 mM in sodium bicarbonate were tested for their effect on RNA-directed DNA (R-DNA) and DNA-directed DNA (D-DNA) polymerase activity of murine sarcoma virus (MSV) strains H and M, feline leukemia virus (FeLV) and avian myeloblastosis virus (AMV). R-DNA polymerase was assayed by measuring incorporation of <sup>3</sup>H-thymidine triphosphate (TTP) into DNA of a suspension of 20 µl virus pretreated with 10 µl 0.1% NP40 detergent (15 min, 0°C) followed by 2 µl rifamycin derivative (15 min, 37°C). D-DNA polymerase was assayed in a similar manner except that purified viral polymerase was used instead of whole virus. Of the 37 rifamycin derivatives tested, 29 3-cyclic amine derivatives were good inhibitors of viral R-DNA and D-DNA polymerases (e.g., 99% inhibition of MSV H strain polymerases at 50 µg/ml and 70% at 20 µg/ml). Five derivatives containing a cyclohexyl or cyclohexylalkyl substituent on the piperidine ring (C20, C22, C23, C27, C31) were especially active (90% inhibition at 20 µg/ml), being four to five times more active than piperidyl derivatives bearing a phenyl group (C19, C21, C30). The benzoxazino and guinoxalino derivatives were only moderately effective. The seven most active inhibitors (C10, C11, C20, C22, C23, C27, C31) inhibited FeLV R-DNA polymerase 80-99% at 100 µg/ml, 50-91% at 50 µg/ml and 20-60% at 10 µg/ml. Penetration of these compounds into AMV was found to be rate-limiting, as 100 µg/ml would

produce 89-99.9% inhibition in partially disrupted AMV but had no effect on intact virus. Those 3-amine derivatives most active against viral polymerase inhibited MSV-induced transformation of Balb/3T3 cells by 90-100% (10 µg/ml) and 30-100% (5 µg/ml). Transformation could be due to other effects, since cell multiplication was inhibited in most instances. The seven derivatives which inhibited both viral polymerase and cell transformation could also inhibit partially purified DNA polymerase of human KB cells but only at concentrations five to ten times higher than those required to inhibit viral polymerase under the same conditions.

1731 RESCUE OF THE GENOME OF FOCUS FORMING VIRUS FROM RAT NON-PRODUCTIVE LINES BY 5'-BROMODEOXYURIDINE. (E.) Klement, V. (U. Southern California Sch. Med., Los Angeles), M. O. Nicolson and R. J. Huebner. *Nature New Biol* 234(44):12-14, 1971.

Successful induction of focus forming virus in permissive non-productive cells by treatment with the mutagen 5'-bromodeoxyuridine (BUdR) is reported; no exogenous helper virus was introduced. Non-productive normal rat kidney cells (NP) which had been transformed by Kirsten mouse sarcoma virus (K-MSV) were maintained in seven monocellular clones. NP cells were treated with BUdR, and all seven treated clones yielded focus-forming virus. The titer of virus released from NP clones depended on the concentration of BUdR and on the time of exposure. The lowest concentration of BUdR to induce viral synthesis was 10<sup>-6</sup>M. With 10- and 100-fold increases of the drug dose, the virus yield increased but beyond that (10<sup>-3</sup>M) the higher concentrations were toxic for the cells and virus yield decreased. The BUdR-induced virus could transform NRK cells but not mouse embryo cells of NIH Swiss and BALB/c origin. The type specific antigenicity of chemically induced virus was different from that of K-MSV. The physical characteristics of the BUdR-induced virus indicated that the virus was similar to the murine leukemia-sarcoma virus complex. It is thought that chemical induction of virus can be explained by chemical induction of a rat C-type virus which in turn provides the helper function for the sarcoma virus genome.

1732 TRANSFORMATION OF MOUSE 3T3 CELLS BY MURINE SARCOMA VIRUS: RELEASE OF VIRUS-LIKE PARTICLES IN THE ABSENCE OF REPLICATING MURINE LEUKEMIA HELPER VIRUS. (E.) Bassin, R. H. (Nat. Cancer Inst., Bethesda, Md.), L. A. Phillips, M. J. Kramer, D. K. Haapala, P. T. Peebles, S. Nomura and P. J. Fischinger. *Proc Nat Acad Sci USA* 68(7):1520-1524, 1971.

Noninfectious virus-like particles have been identified in two lines cloned from murine sarcoma virus (MSV) positive and murine leukemia helper virus (MULV) negative transformed mouse 3T3 cells (S+L-). The particles, 95 to 105 nm in diameter, were seen under the electron microscope



budding from the host cell membrane, in intracellular membrane-bound vacuoles and in extracellular spaces. Their morphology generally resembled C-type MuLV. Sucrose density gradient analysis of normal cells which had incorporated labelled uridine showed no radioactivity corresponding to MuLV particles. Similar analysis of the cloned cells did reveal such material, even though no replicating MSV or MuLV could be detected. Gradient analysis of extracts from S+L- cells superinfected with MuLV resulted in recovery of infectious MSV and MuLV. Cell lysates and supernatants from the cloned S+L- lines were unable to transform other cells under a variety of favorable conditions. It was concluded that the particles isolated from the two clonal S+L- 3T3 lines may represent a "defective" form of MSV.

- 1733 RESCUE OF MURINE SARCOMA VIRUS FROM A SARCOMA-POSITIVE LEUKEMIA-NEGATIVE CELL LINE: REQUIREMENT FOR REPLICATING LEUKEMIA VIRUS. (E.) Peebles, P. T. (Natl. Cancer Inst., Bethesda, Md.), R. H. Bassin, D. K. Haapala, L. A. Phillips, S. Nomura and P. J. Fischinger. *J Virol* 8(5):690-694, 1971.

The release of infectious murine sarcoma virus (MSV) upon superinfection by murine leukemia virus (MuLV) was studied in a transformed mouse sarcoma-positive, leukemia-negative 3T3 cell line (S+L-) which normally released noninfectious C-type particles. A nine to 12 hr. period elapsed between infection with MuLV and simultaneous release of both MSV and MuLV. Inhibition of DNA synthesis by excess thymidine inhibited replication of MuLV and subsequent rescue of infectious MSV. Results from a variety of experimental conditions indicated that MuLV replication was necessary for MSV rescue and that virion assembly of both MSV and MuLV depended on one or more factors produced late in the course of MuLV replication. A ten-fold excess of infectious MSV over MuLV was recovered 96 hrs. after MuLV infection. Stocks of this sample were used to produce new S+L- lines by end point titration methods.

- 1734 PRESENCE OF SARCOMA GENOME IN A "NON-INFECTIOUS" MAMMALIAN VIRUS. (E.) Gazdar, A. F. (Natl. Cancer Inst., Bethesda, Md.), L. A. Phillips, P. S. Sarma, P. T. Peebles and H. C. Chopra. *Nature New Biol* 234(46):69-72, 1971.

A strain of murine sarcoma virus (MSV) isolated from a spontaneous tumor in a hybrid New Zealand mouse was found to induce sarcomas in mice, rats, and hamsters rapidly. Two sarcomas induced in hamsters were isolated and cultured as lines HTG1 and HTG2. Virus production in the cell lines was studied; it was found that type C particles were present in the extracellular spaces, intracytoplasmic vacuoles, and in buds around the cell periphery. Tritiated uridine analyses indicated that particles in the density range of viral RNA were present. These particles were purified and subjected to MSV rat antiserum; the HTG2 line was found to be related antigenically

to MSV. However, such particles alone were incapable of producing tumors *in vitro* in NIH Swiss, BALB/c secondary embryo, or continuous Swiss 3T3FL mouse lines, or in secondary hamster embryo cells or normal rat kidney tissues. If virus particles released by HTG1 and HTG2 cells were a type of MSV with an altered host range, co-sedimentation with a leukemia virus could be expected to form interviral aggregates possessing the transforming capacity of MSV and the host range of the leukemia virus. Virus from HTG2 cells was co-sedimented with a strain of a murine leukemia virus which transforms 3T3FL mouse cells; the co-sedimented pellets transformed 3T3FL and inoculation of the pellets into BALB/c mice induced sarcomas.

- 1735 THE KINETICS OF RESCUE OF THE MURINE SARCOMA VIRUS GENOME FROM A NONPRODUCER LINE OF TRANSFORMED MOUSE CELLS. (E.) Rowe, W. P. (Natl. Inst. Allergy Infectious Dis., Natl. Inst. Hlth., Bethesda, Md.) *Virology* 46(2):369-374, 1971.

The Moloney sarcoma virus (MSV)-8 line of Moloney sarcoma virus-transformed BALB-3T3 mouse cells was incubated with Moloney leukemia virus (MLV). The culture medium was removed, the cells were irradiated, and the nonproducer NIH strain of mouse embryo cells was overlaid. These mouse embryo cells replaced the dying MSV-8 cells, but formed typical MSV foci while doing so. These foci were counted, and the NIH cells were exposed to UV; XC cells were overlaid to develop the leukemia virus plaques. It was therefore possible to perform quantitative and temporal studies of rescue process. It was found that the MSV genome could be rescued both efficiently and rapidly; the sarcoma genome was rescued from about 50% of the cells in the first cycle of infection. Cells producing MLV also produced MSV, the formation of the two viruses on the individual cells occurring simultaneously; this was evidenced by the fact that there were almost no MSV foci which did not register as MLV plaques. There were found to be no detectable number of cells producing only sarcoma virus. Therefore, the MSV genome in the nonproducer cell was present in a form which was readily, rather than sporadically, available for rescue.

- 1736 TRANSFORMATION OF MAMMALIAN CELLS *IN VITRO* BY ROUS SARCOMA VIRUS. (Jap.) Sekiya, S. (Sch. Med., Chiba U., Japan), T. Kuwata and K. Nakamura. *Med Biol* 83(1):35-40, 1971.

Mouse (18 day), hamster (13 day) and human (three month) embryonic cells were transformed *in vitro* using Rous sarcoma virus, Schmidt-Ruppin strain. The viral infection was performed by mixing chick sarcoma cells with the various embryonic cells and incubating them until transformed cells were obtained. The transformation was examined by observing the following parameters: tumor production in newborn isogenic animals which had been inoculated with transformed cells; tu-

mor production in the cheek pouch of the cortisone acetate-treated young hamster, and colony production in agar medium. In the mouse cells, some morphological changes were noted at the third month of mixed cultivation, but only at the ninth month was transformation noted. Although no virus was found in the transformed cells, viral genome, tested by inoculating it into the commercially available newly hatched white Leghorn, was present in the cells. Transformation took place in the hamster cells two months after mixed cultivation. Again, the viral genome was found in the cells. In spite of the facts that the cells showed some morphological changes and that they contained the viral genome after three months of cultivation, none of the human cells gave positive results in colony production in the agar medium or in tumor production in the hamster cheek pouch. In contrast to the semi-permanent proliferative ability of the transformed cells of mouse and hamster, the human cells could not be cultured longer than five months regardless of the virus treatment. While no spontaneous transformation was seen in either mouse or human cells, it was seen in the hamster cells after 710 days of cultivation.

- 1737 A MUTATION IN A ROUS SARCOMA VIRUS GENE THAT CONTROLS ADENOSINE 3',5'-MONOPHOSPHATE LEVELS AND TRANSFORMATION. (E.) Otten, J. (Nat'l. Cancer Inst., Bethesda, Md.), J. Bader, G. S. Johnson and I. Pastan. *J Biol Chem* 247(5):1632-1633, 1972.

Cultured chick embryo cells were infected with a temperature-sensitive mutant of the Bryan strain of Rous sarcoma virus (RSV-Ta). RSV-Ta is capable of infecting cells and replicating at both 40.5°C and 36°C; however, at 40.5°C it is unable to transform the cell. When dibutyryl-cAMP (Bt<sub>2</sub>-cAMP) (1.2 mM) and theophylline (1 mM) were added to infected chick cell cultures at 40.5°C two hr before the temperature was lowered to 36°C, the cells retained their normal morphology for at least the following 12 to 24 hr. Phosphodiesterase inhibitors partially blocked the transformation at 36°C. Papaverine (0.2 mM) or 1-methyl-3-isobutylxanthine (1 mM) each in combination with Bt<sub>2</sub>-cAMP (1.2 mM) completely blocked transformation. Adenosine monophosphate showed no blocking effect. In infected cells at 40.5°C, the level of cAMP was in the range of normal cells (197±15 pmoles per µg nucleic acid) but when cells were shifted to 36°C for 12 hr, cAMP levels fell dramatically (20 pmoles per µg of nucleic acid). Levels of cAMP were low in cells transformed by wild-type RSV at both temperatures (34 to 39 ± 3 pmoles per µg of nucleic acid). Levels of cAMP in normal fibroblasts were unaffected by temperature (210 pmoles per µg of nucleic acid). Within 20 min after changing infected cells from a temperature of 40.5°C to 36°C, the level of cAMP fell by about 50%. Levels remained in this range for approximately six hr. After 12 hr cAMP levels again began to decrease. These results suggest that an early event in transformation leads to a decreased level of cAMP, and the decreased cAMP level results in some of the unique properties of transformed cells.

- 1738 SURFACE GLYCOPROTEINS AND GLYCOLIPIDS OF CHICKEN EMBRYO CELLS TRANSFORMED BY A TEMPERATURE-SENSITIVE MUTANT OF ROUS SARCOMA VIRUS. (E.) Warren, L. (Imperial Cancer Res. Fund Lab., London, England), D. Critchley and I. Macpherson. *Nature* 235(5336):275-278, 1972.

Surface glycoproteins and glycolipids were analyzed in chicken embryo cells transformed by a temperature-sensitive Rous sarcoma virus (RSV) strain T5. Chicken embryo cells transformed by T5 are morphologically like cells transformed by wild type RSV(SR) at 35°-36°C but lose their transformed morphology at 41°C. A dual label technique was used to compare surface glycoproteins of normal and T5-transformed cells. <sup>14</sup>C-Fucose was added to normal cell cultures and <sup>3</sup>H-fucose was added to transformed cultures one day after cells were shifted to 35° or 42°C. The cells were trypsinized 72 hr after addition of isotope before they became confluent. Pronase-digested "trypsinates" of <sup>14</sup>C-labeled control cells and <sup>3</sup>H-labeled RSV(SR)- or T5-transformed cells were mixed and chromatographed together on Sephadex G-50. Cell surface material from cells transformed by T5 and grown at 35°C displayed an elution pattern similar to that seen with cell surface material from wild type RSV(SR)-transformed cells grown at either 35° or 41°C. The larger surface material characteristic of RSV(SR)-transformed cells and T5-transformed cells grown at 35°C disappeared when T5 cells were shifted to 41°C. Similar results were obtained when RAV 1-transformed cell surfaces were analyzed, indicating that the presence of carbohydrate-containing proteins of larger size on the surface of cells is associated with transformation rather than with a particular virus infection. Normal and transformed cells labeled with <sup>14</sup>C-palmitate were also analyzed for their total neutral lipids, phospholipids and glycolipids by thin-layer chromatography. No marked difference in incorporation of isotope into glycolipids of normal and RSV(SR)-transformed cells was found at either 35° or 41°C. Ceramide monohexoside and hematoside were the major glycolipids present. The results thus confirm previous reports that the surface of virus-transformed cells have relatively large amounts of fucose-containing glycoproteins. The mechanism of increase is unknown.

- 1739 COMPARATIVE PROPERTIES OF RNA AND DNA TEMPLATES FOR THE DNA POLYMERASE OF ROUS SARCOMA VIRUS. (E.) Duesberg, P. (Dept. Molec. Biol., U. California, Berkeley), K. V. D. Helm and E. Canaani. *Proc Nat Acad Sci USA* 68(10):2505-2509, 1971.

Template activities of various RNAs for purified Rous sarcoma virus (RSV) RNA-dependent DNA polymerase were quantitatively compared in the presence or absence of competing oligonucleotides. Five times more DNA was synthesized by the polymerase when purified 60-70S RSV RNA was used as template than when heat-dissociated RSV RNA, influenza RNA, or tobacco mosaic virus (TMV) RNA were used as templates. Template activity of denatured salmon DNA was 1.3 times, and that of poly(dAT) was about three times that of 60-70S RSV



RNA. RSV DNA polymerase was nonspecific for RSV RNA, since 60-70S RNA from several other avian tumor virus RNAs showed similar template activities. Template activities of natural RNAs were increased significantly by oligo(dT) or oligo(dC). Both oligo(dT) and oligo(dC) could restore template activity of heat-dissociated RSV RNA to that of native 60-70S RSV RNA. Substrate deletion experiments indicated that there might be an A-rich sequence in the template RSV RNA. These results indicated that RSV DNA polymerase preferred partially double-stranded or hybrid regions of RNA for optimal activity, although certain single-stranded regions could also serve as template. Poly(dAT) inhibited RSV RNA-dependent DNA synthesis by RSV DNA polymerase, a finding consistent with the hypothesis that RNA- and DNA-dependent DNA synthesis involved at least one common active site on the same enzyme or enzyme complex.

- 1740 ADENYLIC ACID-RICH SEQUENCE IN RNAs OF ROUS SARCOMA VIRUS AND RAUSCHER MOUSE LEUKAEMIA VIRUS. (E.) Lai, M. M. C. (Dept. Molec. Biol., U. California, Berkeley, Calif.) and P. H. Duesberg. *Nature* 235(5338):383-386, 1972.

The Prague strain of Rous sarcoma virus (P-RSV) was analyzed to demonstrate the presence of adenylic acid (A)-rich sequences in the viral RNA. P-RSV RNA was labeled with  $^3\text{H}$ -adenylic acid and subjected to enzyme digestion, electrophoretic mobility studies, and velocity sedimentation techniques. Nine percent of the adenosine of P-RSV RNA was found in an RNA-ase resistant, A-rich sequence, the whole probably existing as a single-stranded helical structure. In addition, most of the total viral RNA containing A-rich sequences were discovered to be situated in the slowly sedimenting fractions between 4 and 12S, thus indicating that the A-rich RNA derives from the degradation of 60-70S RNA. Further studies on P-RSV RNA-binding to Millipore filters and on sedimentation distribution confirmed these results. Rauscher mouse leukemia virus (MLV) RNA studies yielded results similar to those of P-RSV RNA: influenza virus RNA, however, did not contain A-rich sequences. It is speculated that the tumor virus RNA is replicated in the nucleus and that the A-rich sequences are involved in transporting mRNA from the nucleus to the cytoplasm.

- 1741 ELEVATED GLYCOSIDASES AND PROTEOLYTIC ENZYMES IN CELLS TRANSFORMED BY RNA TUMOR VIRUS. (E.) Bosmann, H. B. (U. Rochester Sch. Med. Dent., N.Y.). *Biochim Biophys Acta* 264(2):339-343, 1972.

Four fibroblast cell lines were analyzed for activities of nine glycosidases and two proteases. The four lines were 3T3-Va (an established embryonic mouse line), Balb/3T3 (a 3T3 clone), MSV-3T3 (murine sarcoma virus-transformed 3T3) and RSV-3T3 (Rous sarcoma virus-transformed 3T3). Enzyme activity was analyzed in partially purified cell homogenates. Glycosidase, acid phosphatase and  $\beta$ -glucuronidase activity were determined at pH 4.3 and 37°C by spectrophotometric measurement of p-nitrophenol which

was enzymatically split from the p-nitrophenol derivative of the substrate. Proteolytic activity was measured by the degree of enzymatic degradation of  $^3\text{H}$ -acetylated hemoglobin. Glycosidase (glucosidase, galactosidase, mannosidase, fucosidase, xylosidase, N-acetyl-B-glycosaminidase), B-glucuronidase, acid phosphatase and proteolytic levels in 3T3-Va and Balb/3T3 cell lines were essentially the same. In every instance, however, (except  $\alpha$ -fucosidase and  $\beta$ -xylosidase) much higher levels of glycosidases were found in the RNA tumor virus-transformed cells (MSV-3T3 and RSV-3T3). Proteolytic (pH 3.4 cathepsin-like and pH 7.4 trypsin-like) activity was similarly elevated in the MSV- and RSV-3T3 cells. Acid phosphatase and B-glucuronidase were not elevated in transformed cells. Enzyme assays on mixtures of cell extracts showed that activity was essentially additive between the normal and transformed cells thus indicating that the observed differences between normal and transformed cells were not due to inhibitors, activators or cofactors. It is concluded that elevations in glycosidase and protease are a general phenomenon of transformation and are not limited to transformation by DNA viruses.

- 1742 CELL TRANSFORMATION INDUCED BY ROUS SARCOMA VIRUS: ANALYSIS OF DENSITY DEPENDENCE. (E.) Weiss, R. A. (Dept. Anat., U. College, London, England). *Virology* 46(2):209-220, 1971.

When trypsinized chick embryo cells were seeded onto an established monolayer of chick embryo cells they divided at least once. They did not divide, however, when seeded onto a stationary monolayer of mouse cells. It is suggested that the mouse cells provide a surface component which prevents the chick embryo cells from dividing. When Rous sarcoma virus (RSV) infected chick embryo cells were seeded onto stationary mouse cells transformation was repressed because the cells did not undergo the division that is necessary for the expression of transformation. This suppression of transformation by RSV was unrelated to the susceptibility of the inhibiting cell layer to infection with RSV. Cells of other avian species (quail, pheasant, goose) did not inhibit transformation of RSV infected cells. Chick cells freshly infected or fully transformed with RSV were seeded onto dense layers of mouse or chick cells that were resistant to RSV. After six days the cultures were trypsinized and the total number of RSV infected cells was determined by focus assay. There was no replication of the underlying cells that were initially seeded at very high density. While the growth of the fully transformed Rous cells was retarded by these high density chick and mouse cultures several divisions occurred. No growth of the freshly infected chick cells occurred on dense mouse cells but, on the dense chick cells there were as many transformed cells as in the cultures seeded with fully transformed Rous cells. The effect of culture age rather than cell density was examined by adding RSV or RSV infected cells at different times after seeding the underlying layer. During the first 72 hours there was little decrease in focus-forming efficiency by the RSV infected cells. However, there was a marked decrease in

focus formation when the cells were directly infected by RSV. The decrease in focus formation and in the number of infected cells occurring as the virus infected cultures aged, occurred both in sparsely and densely seeded cultures.

- 1743 SPONTANEOUS SEGREGATION OF NONTRANSFORMING VIRUSES FROM CLONED SARCOMA VIRUSES. (E.) Vogt, P. K. (U. Washington Sch. Med., Seattle,). *Virology* 46(3):939-946, 1971.

It is known that strains of Rous sarcoma virus (RSV) may be the source of nontransforming (NT) viruses. A study was performed to determine the incidence and levels of such NT viruses in various strains of helper independent avian sarcoma viruses, and to examine the possibility that the presence of NT viruses is the result of passage through group-specific antigen (gs) positive chicken cells. It was determined by seeding and challenging techniques that NT virus could be detected in the presence of excess sarcoma virus when cloned on gs-negative chick embryo fibroblasts. NT virus was then isolated in six out of seven of the clones, NT virus occurrence was between 4 and 17% of the sarcoma virus concentration. It was found that the NT virus had plating efficiencies and host ranges identical to the sarcoma viruses; in addition, the envelopes of both NT and sarcoma viruses were the same. Thus, NT viruses are probably spontaneous mutants occurring regularly and inevitably during sarcoma virus replication; the emergence of such viruses, therefore, do not require the induction of a resident leukosis virus.

- 1744 EFFECT OF DISTAMYCIN A AND CONGOCIDINE ON DNA SYNTHESIS BY ROUS SARCOMA VIRUS REVERSE TRANSCRIPTASE. (E.) Kotler, M. (Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel) and Y. Becker. *FEBS Letters* 22(2):222-226, 1972.

The effect of the antibiotic, congocidine, (which resembles Distamycin A) on the activity of purified Rous Sarcoma Virus (RSV, B77 strain) reverse transcriptase and the effect of Distamycin A (a basic oligopeptide antibiotic) on the nature of the DNA molecules synthesized *in vitro* by RSV enzyme were studied. DNA synthesized by reverse transcriptase in the absence or presence of either antibiotic (100 µg/ml reaction mixture) was studied by elution from hydroxyapatite columns using purified <sup>14</sup>C-labeled herpes simplex virus DNA as marker. Both antibiotics inhibited synthesis of DNA by RSV reverse transcriptase. The effect of Distamycin A was much more pronounced (50% inhibition) than that of congocidine (about 20% inhibition). Distamycin A markedly affected, but did not prevent, synthesis of DNA by RSV enzyme when added to the enzymatic reaction prior to initiation of DNA synthesis. <sup>3</sup>H-TMP incorporation in the presence of antibiotic continued for 30 min. and then stopped whereas incorporation in controls continued for 60 min. Addition of Distamycin A (25 µg/ml and 100 µg/ml) five min after initiation of DNA synthe-

sis also markedly affected DNA synthesis although <sup>3</sup>H-TMP incorporation continued for ten to 20 min. The effects of Distamycin A on RSV enzyme thus differed from those of rifampicin, which was shown to inhibit DNA synthesis completely, but resembled the inhibitory effect of actinomycin D. Analysis of the DNA species synthesized by reverse transcriptase in the presence of Distamycin A (100 µg/ml) showed that ssDNA (single stranded DNA present in untreated RSV) and hyDNA (RNA:DNA hybrids normally present in RSV), but not dsDNA species (double stranded DNA molecules present in untreated RSV), were synthesized. Distamycin A apparently inhibited the enzymatic step necessary to form dsDNA from ssDNA and did not affect the synthesis of HyDNA and ssDNA. Congocidine (100 µg/ml) decreased <sup>3</sup>H-TMP incorporation by treated viral enzyme but all three DNA species were still synthesized. It is concluded that the higher antiviral activity of Distamycin A is due to the increased number of pyrrole rings as compared to congocidine. The nature of the side chain on the molecule also is important in determining antiviral activity. Distamycin A might represent a group of antibiotics with activities against oncornavirus reverse transcriptase.

- 1745 RIBONUCLEASE-SENSITIVE DEOXYRIBONUCLEIC ACID POLYMERASE ACTIVITY IN UNINFECTED RAT CELLS AND RAT CELLS INFECTED WITH ROUS SARCOMA VIRUS. (E.) Coffin, J. M. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and H. M. Temin. *J Virol* 8(5):630-642, 1971.

A fibroblast cell line derived from Sprague-Dawley embryo rats (designated R) was infected with the B77 strain of Rous sarcoma virus. No virus particles were detected as being shed from the cells when the supernatant fluid from the inoculated culture was analyzed, but the rat fibroblasts still contained the B77 genome. Since it was known by annealing techniques that the B77 genome would hybridize with chicken cell RNA, further studies were carried out to determine whether such a hybridization would occur with the R(B77) line. The R(B77) cells were disrupted and the RNA-directed DNA polymerase particles were isolated by density gradient centrifugation. The DNA polymerase was labeled, extracted and annealed with the B77 strain virus RNA, but no hybridization resulted. Further annealing studies with uninfected cells produced a 10% hybridization, suggesting that some of the RNA template of the endogenous DNA polymerase reaction was also present in similar fractions of uninfected rat cells. Further characterization of the DNA polymerase showed that activity was similar in both infected and uninfected cells; in addition, all four deoxyribonucleoside triphosphates were found to be necessary for full activity. The endogenous template for the DNA polymerase particle activity from the R(B77) cells was not related to B77 virus RNA or to RNA of the rat C-type particle. These particles may present a chance association between a cell DNA polymerase and cell RNA, or they may be related to an RNA-directed DNA polymerase in normal development.



1746 SYNCHRONIZATION OF ROUS SARCOMA VIRUS PRODUCTION IN CHICK EMBRYO CELLS. (E.)

Leong, J. A. (Dept. Microbiol., U. California, San Francisco), W. Levinson and J. M. Bishop. *Virology* 47(1):133-141, 1972.

Chick embryo fibroblast cultures were inoculated with the radioactively-labelled Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV). When infection was complete, cell cycle analyses, via autoradiography, were carried out and it was found that uninfected fibroblasts and SR-RSV-infected fibroblasts both had similar cell cycles. Inoculated cultures were synchronized, pulse-labelled with tritiated uridine, and subjected at various intervals to isopycnic centrifugation. Results showed that virus release and virus specific RNA and protein synthesis were restricted to the G<sub>1</sub> and early S phase respectively. This conclusion was based on the assumptions that viral RNA and cellular RNA synthesis draw nucleotides from the same pool, and that the time lag between viral RNA synthesis and the appearance of mature virions in the culture medium does not vary with the cell cycle. Since these viral processes occur only during a part of the cell cycle, it appears that they are dependent on some cellular function(s). Evidence indicates that the synchrony of transformed cells was achieved by the low pH of the medium rather than by the withdrawal of serum.

1747 IDENTIFICATION OF THE SPIKE PROTEINS OF ROUS SARCOMA VIRUS. (E.) Rifkin,

D. B. (Rockefeller U., New York, N.Y.) and R. W. Compans. *Virology* 46(2):485-489, 1971.

The Schmidt-Ruppin D strain of Rous sarcoma virus (RSV) grown in chick embryo fibroblast cultures was purified, radioactively tagged, and studied to identify the spike proteins. Purified radioactive RSV was incubated with bromelain for three hours, and re-purified. Electron microscopy, acrylamide gel electrophoresis, and autoradiography of polyacrylamide gels showed that viral glycoproteins were localized at the outer surface of the virion, and were probably associated with spikes. Knoblike projections on the surface of the virion could be removed by exposure to bromelain. The infectivity of bromelain-treated RSV was reduced 10,000-fold by comparison to the infectivity of non-bromelain-treated RSV.

1748 ON THE GENETIC RESISTANCE OF CELLS TO AVIAN TUMOUR VIRUSES. (E.) Kuznetsov, O.

K. (USSR Ministry Publ. Hlth., Leningrad) and A. M. Dyadjkova. *Neoplasma* 19(1):27-31, 1972.

The uptake of Rous sarcoma virus (RSV) strain D-5 or pseudotype RSV (RAV-1) into chick or BALB/c mouse cells genetically resistant or sensitive to infection is studied. After 1, 6, 24 and 72 hr. the cells were fixed and analyzed by the indirect immunofluorescent method using intermediate rabbit serum ob-

tained through immunization of the animals by cultured Rous virus. Viral antigen was detected in less than two percent of sensitive chick cells at one and six hr. post-infection. Viral antigen was present in 60 to 80% of sensitive cells at 24 hr. and in 97 to 99% of sensitive cells at 72 hr. Infectious virus was detected in all sensitive cultures. Exactly the opposite pattern was seen in resistant cells. Viral antigen was detected in ten to 60% of insensitive chick or mouse cells at one and six hr. post-infection as fluorescent granules localized in the cytoplasm near the external cell membrane, or throughout the whole cytoplasm. Less than three percent of the insensitive cells showed fluorescence at 24 and 72 hr. No infectious virus was observed in either the culture fluid or in the insensitive cells. Since the immunofluorescent method used detected external virus coat protein, the results indicated the presence of intact viral particles in infected resistant cells. Since viral antigen persisted in resistant cells for six hr., it was suggested that uncoating of the virus and release of viral nucleic acid were delayed, thus viral replication could not proceed.

1749 THE EFFECTS OF RECIPROCAL CHANGES IN TEMPERATURE ON THE TRANSFORMED STATE OF CELLS INFECTED WITH A ROUS SARCOMA VIRUS MUTANT. (E.) Kawai, S. (Public Hlth. Res. Inst. City New York, N. Y.) and H. Hanafusa. *Virology* 46(2):470-479, 1971.

This paper describes the basic characteristics of a temperature-sensitive mutant virus and the behavior of cells infected with the virus under various physiologic conditions. Mutagenized viruses were obtained from stock Schmidt-Ruppin strain Rous sarcoma virus by treatment with 5-fluorouracil and then inoculated into C/O or C/O' type chick embryo cell cultures. Cloning studies on the infected embryo cells indicated that five separate clones could produce temperature-sensitive transformed cells. One such virus, Ts-68, was isolated and used for specific experimental studies, along with the wild type virus; tests were conducted at 37° and 41° C. Wild-type virus could induce focus transformation and colony formation at both temperatures, and could readily induce tumors when it was given to chickens (body temperature approximately 41° C) *in vivo*. On the other hand, Ts-68 was highly temperature-dependent. The cells maintained at 37° C behaved like the wild-type, but at 41° C focus formation was inhibited, cell growth was greatly reduced, and tumor production *in vivo* was both suppressed and delayed; in addition, sugar consumption from the media by infected cells was reduced and the rate of virus production was initially slowed. These aberrant conditions, however, were all found to be reversible when the cells were incubated at 37° C; the cells took on the transformed appearance and behaved, for all practical purposes, like the wild-type cells and like the cells continuously incubated at 37° C. It was also discovered that biochemical inhibitors, particularly puromycin and cycloheximide, could inhibit transformation shift upon temperature change and that 37° C-maintained cells could revert to the 41° C type if the media was unchanged for a

long period. It is therefore postulated that a virus-coded, nonstructural protein which is temperature sensitive plays an essential role in cell transformation. This heat-sensitive protein formed in the mutant-infected cells may be somewhat unstable and consequently continuous synthesis of this molecule would be required to maintain the transformed state.

- 1750 ADENYLATE CYCLASE AND PHOSPHODIESTERASE ACTIVITY OF NORMAL AND SV<sub>40</sub> VIRUS-TRANSFORMED HAMSTER ASTROCYTES IN CELL CULTURE. (E.) Weiss, B. (Natl. Inst. Mental Hlth., Washington, D.C.) H. M. Shein and R. Snyder. *Life Sci* 10(21):1253-1260, 1971.

Cyclic 3',5'-adenosine monophosphate (cyclic 3',5'-AMP), a biomedical mediator in animal cells is catalyzed by adenylate cyclase and hydrolyzed by phosphodiesterase. Such enzymatic activity has been reported as necessary for the smooth functioning of the brain; therefore, the presence of these enzymes in the principal glial cell types, astrocytes and oligodendrocytes, was determined. Studies were carried out on tissue cultures of normal newborn hamster brain astrocytes, SV<sub>40</sub>-transformed newborn hamster astrocytes, and normal newborn hamster fibroblasts. A comparative analysis was done between these and normal adult hamster cerebrum cells. It was found that the activities of both enzymes were of the same order of magnitude in both normal astrocytes and whole cerebrum. However, in SV<sub>40</sub>-transformed astrocytes, the level of phosphodiesterase was similar to that in normal astrocytes, while the adenylate cyclase activity was less than one half. Normal and neoplastic astrocytes contain the enzymatic machinery needed for synthesis and hydrolysis of cyclic 3',5'-AMP, thus indicating a possible mechanism for communication of neurons with astrocytes.

- 1751 REINITIATION WITHIN ONE CELL CYCLE OF THE DEOXYRIBONUCLEIC ACID SYNTHESIS INDUCED BY SIMIAN VIRUS 40. (E.) Hirai, K. (Wistar Inst., Philadelphia, Pa.), J. M. Lehman and V. Defendi. *J Virol* 8(6):828-835, 1971.

Semiconfluent secondary Chinese hamster embryo (ChH) cell cultures were infected with simian virus 40 (SV40) and were labelled 2 hr later with 5-bromodeoxyuridine. DNA was then extracted and subjected to density gradient equilibrium centrifugation. It was found that DNA could be isolated into three bands: light (LL) molecules; intermediate (HL) molecules; and heavy (HH) molecules. The proportion of the heavy molecules varied from 13 to 25%. The occurrence of tetraploid mitosis indicated that two cycles of DNA synthesis had occurred, in which recycling through mitosis was inhibited. This finding was corroborated by the following: the newly synthesized HH DNA was essentially cellular; and the size of the HH DNA was calculated to be  $15 \times 10^6$  daltons

or higher. Analysis of the kinetics indicated that the heavy DNA resulted from the reinitiation of DNA synthesis after the initial replication of the entire cell DNA was completed

- 1752 SPECIFIC CLEAVAGE OF SIMIAN VIRUS 40 DNA BY RESTRICTION ENDONUCLEASE OF HEMOPHILUS INFLUENZAE. (E.) Danna, K. (Johns Hopkins U. Sch. Med., Baltimore, Md.) and D. Nathans. *Proc Nat Acad Sci USA* 68(12):2913-2917, 1971.

Small-plaque SV40 virus of strain 776 was purified on African green monkey kidney cells of the line CV-1, and was later propagated in African green monkey kidney cells of the line BSC-1. When enough stock virus was finally accumulated, the DNA was labeled, extracted, and subjected to digestion by the endonuclease of the bacteria *Haemophilus influenzae*. It was found that the bacterial enzyme produced several double-stranded breaks in the homogeneous SV40 DNA. The resulting fragments of these breaks were resolved by polyacrylamide gel electrophoresis into 11 distinct peaks, eight of which were equimolar. The peaks were then analyzed by electron microscopy, and by radioactive techniques. The fragments ranged from  $6.5 \times 10^5$  to  $7.4 \times 10^4$  daltons.

- 1753 SUSCEPTIBILITY OF UNFERTILIZED AND FERTILIZED MOUSE EGGS TO SIMIAN VIRUS 40 AND MOLONEY SARCOMA VIRUS. (E.) Sawicki, W. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), W. Baranska and H. Koprowski. *J Nat Cancer Inst* 47(5):1045-1052, 1971.

Unfertilized mouse eggs infected with SV40, SV40 DNA or Moloney sarcoma virus (MSV) at the one-cell stage and cultivated *in vitro* for three to four days showed no abnormal morphological or developmental changes. At the two-cell stage, mouse embryos infected with SV40 DNA showed retarded development. Morula stage SV40 DNA-infected cells developed normally into the blastula stage. Infection by MSV of either two-cell fertilized eggs or morulae showed no effects. Rescue of infectious SV40 or MSV could be effected by growing infected cells with susceptible somatic cells for three to four days.

- 1754 STUDIES ON THE TRANSFORMATION OF HUMAN FETAL CELL CULTURES BY SIMIAN VIRUS 40. (E.) Nishida, S. (Okayama U. Med. Sch., Japan). *Acta Med Okayama* 24(4):417-434, 1970.

This study describes two independent transformation experiments using simian virus (SV40) as an infectious agent of human cells. Two cell series were derived from a human male three-month-old fetus; once established in culture both series were inoculated with SV40 three times for two hours within either 45 or 21 days. The morphology of both cell series after infection and transformation was similar; the infected cultures showed numerous mitoses, pleomorphic nuclei with many nucleoli, loss of contact inhibition, lower



growth rate, and loss of cells. It was found that T antigen was present in 6% of the cell series inoculated over the 45-day period, while V antigen levels fluctuated over the length of the study. On the other hand both T and V antigens were present at considerably lower levels in the cells exposed over a 21-day period, but behaved in the same relative manner. Immunofluorescence studies on both cell series confirmed this and indicated that the antigens were located mainly in the nuclei. Electron microscopic studies of transformed cultures showed round, uniform intranuclear particles in crystalline arrangements. When the chromosomes were analyzed, it was discovered that transformed cells were hypodiploid, with abnormal chromosomes consisting of dicentric and with secondary constrictions; however, there were no marker chromosomes. Infectivity titers were found to be  $10^4$  TCID<sub>50</sub>/0.2 ml for the 45- and 21-day inoculation period respectively. Transplantation tests on the hamster cheek pouch produced no neoplastic growths but did induce nodules of granulation tissue containing necrotic debris and leucocytes in a few cases. It has been established that human cells can be transformed by SV40 if multiple inoculations are carried out over a period of time.

- 1755 DIRECT ISOLATION AND CHARACTERIZATION OF "FLAT" SV40-TRANSFORMED CELLS. (E.) Scher, C. D. (Natl. Cancer Inst., Bethesda, Md.), and W. A. Nelson-Rees. *Nature* 233(43):263-265, 1971.

SV40-transformed BALB/c-3T3 mouse embryo lines were grown in serum factor-free medium and subsequently were cloned. The transformed cells thus derived had disoriented growth patterns, possessed T antigen and exhibited a spectrum of saturation densities. Fifteen percent of the clones isolated were "flat" revertants exhibiting relatively low saturation densities which were approximately the same as those of the nontransformed 3T3 cells. Five out of six "flat" lines synthesized DNA at confluency with 50 to 70% of the cells incorporating <sup>3</sup>H-thymidine. Only one "flat" transformant line behaved like normal 3T3 cells at confluency, with only about 1% of the cells incorporating <sup>3</sup>H-thymidine. This line was still able to synthesize DNA, since incorporation of <sup>3</sup>H-thymidine could be induced by adding fresh serum to the medium. The only virus altered growth property of these cells was the ability of sparse cells to grow in serum factor-free medium. The saturation density of "flat" transformants that continue to synthesize DNA while confluent is determined by an equilibrium between cell division and cell death; 48% of the cells in a confluent layer of one "flat" transformant line were observed to undergo mitosis, although the total number of cells in the culture remained the same. Previous observations had indicated that "flat" revertants of SV40 and polyoma-transformed 3T3 cells undergo a shift in chromosome number from a hypotetraploid to a hypertetraploid state, with a concomitant increase in the number of metacentrics. However, in this study, three out of four "flat" transformants which continued to syn-

thesize DNA at confluency remained hypotetraploid. Only one line studied showed more than 15% of the cells with one or more metacentric chromosomes. It is thus evident that hypertetraploidy is not a prerequisite for "flat" transformants retaining the ability to synthesize DNA at confluency. It is also evident that low saturation density is not in itself a criterion for density dependent inhibition of cell division.

- 1756 LONGEVITY OF STRAINS FROM INDIVIDUAL FOCI OF HUMAN AMNION CELLS TRANSFORMED BY SIMIAN VIRUS 40. (E.) Fogh, J. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.). *J Nat Cancer Inst* 47(4):733-739, 1971.

The time before "crisis" (or the "longevity") for SV40-transformed human amnion cells increases with the multiplicity of virus exposure of primary cultures. In an attempt to explain this phenomenon, individual transformed foci of human amnion cells were isolated in SV40-infected and transformed primary cultures. Sixteen cell strains derived from individual virus-transformed foci varied in time elapsed between infection and onset of crisis (170-268 days postinfection). There were between 16 and 45 cell divisions before crisis. Twelve days after focus isolation, two pools of cells were prepared from the 16 colony isolates ("pool strains"). The longevity of pool strains was compared with that of strains derived from whole cultures of transformed human amnion cells. It was found that the longevity of a cell strain derived from a culture containing several foci is determined by the longevity of that group of cells in the strain which has the greatest longevity potential (where the "longevity potential" of a cell is its capacity to complete many divisions before "crisis"). Cell morphology differed among strains derived from the various foci. There was no correlation between the morphological character of various strains and longevity.

- 1757 INCREASED UPTAKE OF AMINO ACIDS AND 2-DEOXY-D-GLUCOSE BY VIRUS-TRANSFORMED CELLS IN CULTURE. (E.) Isselbacher, K. J. (Imperial Cancer Res. Fund Lab., London, England). *Proc Nat Acad Sci USA* 69(3):585-589, 1972.

The uptake of isotopically labeled  $\alpha$ -aminoisobutyrate (AIB), glycylglycine (CL), arginine (arg) or 2-deoxy-D-glucose (d-glu) (0.2 to 2.02 mM) into logarithmically growing cultures of baby hamster kidney (BHK) 21, polyoma-transformed BHK 21 (PyJ), BALB/3T3, simian virus 40-transformed 3T3 cells (SV3T3), rat liver (RL), and murine sarcoma virus-transformed RL (MSV-RL) cells was determined by means of a liquid scintillation assay. A 2.5- to 3.5-fold increase in the rate of uptake of AIB, CL and d-glu was observed in the PyJ, SV3T3 and MSV-RL cells, as compared to their nontransformed counterparts; the uptake of arg was five-fold greater in PyJ than in BHK 21 cells. Kinetic analysis suggested that the increased uptake by the virus-transformed cells was associated

with a corresponding three-fold greater  $V_{\max}$  value with no detectable changes in apparent  $K_m$ . The effect of various agglutinins (lectins) on uptake was examined. When PyJ cells were incubated with 100  $\mu\text{g/ml}$  concanavalin A (ConA) or wheat germ agglutinin (WGA), cycloleucine uptake was inhibited 75 and 47%, respectively. This effect could be prevented or modified by the use of appropriate haptens (0.04 M  $\alpha$ -methylglucoside), which bind preferentially to the lectin and presumably displace it from the cell surface. The inhibition produced by ConA could also be reversed by washing cells in phosphate-buffered saline and then incubating them in the presence of  $\alpha$ -methylglucoside. A similar effect was seen by simultaneous or subsequent incubation of the cells with WGA and N-acetylglucosamine (0.04 M). ConA (50 to 300  $\mu\text{g/ml}$ ) decreased AIB uptake by both transformed and untransformed cells to about the same extent (25 to 50% of control). At 50 and 100  $\mu\text{g/ml}$ , WGA inhibited uptake by PyJ cells (48 and 36% of control, resp.) and produced a lesser effect on uptake by BHK 21 cells (60 and 80%, resp.). The same WGA concentrations inhibited AIB uptake into SV3T3 (70 and 58% of control, resp.) but had no effect on uptake by 3T3 cells. It was concluded that increased initial rates of uptake of certain amino acids and sugars may be a feature common to transformed cells, compared to their nontransformed parental controls.

- 1758 A SYMMETRICAL MODEL FOR POLYOMA VIRUS DNA REPLICATION. (E.) Bourgaux, P. (U. Hosp. Ctr., U. Sherbrooke, Quebec, Canada) and D. Bourgaux-Ramoisy. *J Molec Biol* 62(3):513-524, 1971.

Viral DNA was selectively extracted from the TSP-I mutant of polyoma virus. This DNA was subjected to radioactive labeling and then was exposed to nuclease for various lengths of time. It was found, after velocity sucrose gradient centrifugation, that the DNA banded into three different fractions: one at 25S; a second at 19S; and the last at 16S. Upon electron microscopic analysis, it was determined that the 3 DNA fractions were actually different stages of nuclease-induced DNA-digestion. The peak fraction of 25S was found to consist of circular molecules with two branch points, three branches and no end; this was the intact polyoma virus DNA that was unaffected by the nuclease. The 19S fraction was found to be an intermediate product—a ring-shaped duplex with a tail, probably formed by the nuclease digestion of one of the branch points. The 16S fraction was a non-circular duplex (a linear single linkage structure) formed by the digestion by nuclease of both branch points. On the basis of these observations, it is suggested that each branch point is actually a growing point from which the DNA chain is either bidirectionally or unidirectionally replicated.

- 1759 GROWTH AND STIMULATION OF MOUSE TROPHOBLASTIC CELLS IN CULTURE BY POLYOMA VIRUS. (E.) Koren, Z. (Einstein Coll. Med., Bronx, N.Y.),

O. Van Damme, H. Hirumi and K. Maramorosch. *Amer J Obstet Gynec* 111(6):846-50, 1971.

Based on the assumption that the rate of infection produced by an unknown virus might play an important role in the epidemiology of choriocarcinoma, an attempt was made to induce neoplastic transformation of mouse trophoblastic cells. Fertilized ova taken from the fallopian tubes of donor mice, were grafted to the kidneys of recipients of the same strain. Nine to ten days after ova transfer the trophoblastic nodules resulting from these grafts were excised. Minced portions of this tissue (about 0.05 mm in diameter) were put in a culture system and incubated at 37°C in a 5% CO<sub>2</sub>:95% air gas mixture. Seventy-two to 96 hr later the cell cultures were incubated with three strains of virus: 1) polyoma, 2) SV40, and 3) Rous sarcoma (Schmitt-Ruppin). Controls consisting of normal cultures of trophoblastic tissue received the same handling without the virus exposure. Results showed that polyoma virus at a concentration of  $4 \times 10^6$  foci-forming units per ml produced stimulation of mouse trophoblastic tissue in culture. The same result, but in a lesser degree, was obtained with Rous sarcoma virus; no stimulation was seen with the SV40 virus. The virus-treated trophoblastic cells showed morphologic responses such as piling up of cells and multilayer growth as compared to the control cultures which showed only monolayer growth. Cells incubated with polyoma virus were checked by electron microscope for virus particles. Particles resembling polyoma in morphology were observed in the cytoplasm but not in the nuclei of cultured trophoblastic cells. The experiments carried out are evidence that trophoblastic tissue can be transformed into malignant neoplasm; they do not, however, clarify the etiology of choriocarcinoma.

- 1760 VIRUS DNA AND HOST DNA IN POLYOMA VIRUS-INFECTED CELLS AT HIGH TEMPERATURE. (E.) Gilead, Z. (Weizmann Inst. Sci., Rehovoth, Israel). *Virology* 47(1):114-121, 1972.

Mouse kidney cells were established in culture and inoculated with purified SP<sub>2</sub> virus; the cultures were incubated at 41.6°C. The rate of DNA synthesis, normally halted in infected cells at high temperatures, started at 16-18 hr post-infection and reached peak level at 24-38 hr post-infection. Synthesis of infectious SP<sub>2</sub> DNA at 41.6°C was similar to that at normal temperatures during the first half of the infectious cycle; then the synthesis stopped, indicating restricted virus output. When DNA-DNA hybridization was carried out at high temperatures, most of the DNA induced was high molecular weight host DNA. Alternately, viral DNA produced at 41.6°C was of low molecular weight in supercoiled (20S) or nicked (16S) circles or in incomplete, nascent strands and broken fragments.

- 1761 DNA AND GENE THERAPY: TRANSFER OF MOUSE DNA TO HUMAN AND MOUSE EMBRYONIC CELLS BY POLYOMA PSEUDOVIRIONS. (E.) Qasba, P. K. (U. Maryland Sch. Med., Baltimore,) and H. V. Aposhian. *Proc Nat Acad Sci USA* 68(10):2345-2349, 1971.



The transfer of DNA from polyoma pseudovirions (DNA fragments encapsidated by polyoma virus coats) was studied in infected BALB/c mouse and human embryo cells. On the basis of experiments using  $^3\text{H}$ -thymidine-labeled pseudovirus it was found that 24% of total cellular radioactivity appeared in the nuclear fraction of secondary mouse-embryo fibroblasts by 24 hours post-infection. DNA-DNA hybridization studies showed that this radioactivity represents pseudovirus DNA and not contaminating polyoma DNA. Primary human embryo cells were exposed to  $^3\text{H}$ -thymidine-labeled pseudovirions for 24 hr. When cytoplasmic and nuclear fractions were prepared, 7.3% of the total radioactivity found in the cells was associated with the nucleus. Sedimentation of the disrupted nuclear fraction through a neutral sucrose gradient showed that this radioactivity represents uncoated pseudoviral DNA. The pseudoviral DNA in the nuclear fraction has been nicked to some extent, as shown by the heterogeneity of the peaks found after sedimentation of the disrupted nuclear fraction through alkaline sucrose. The experiments demonstrate that polyoma pseudovirions transfer DNA to human cells.

- 1762 POLYOMA VIRUS-INDUCED CELL TRANSFORMATION: ENHANCEMENT WITH TWEEN-80. (Rus.) Irlin, I. S. (N. F. Gamaleya Inst. Epidemiol. Microbiol., Moscow, U.S.S.R.) and I. I. Parkhomenko. *Vop Virus* 16(4):421-424, 1971.

The effect of the surfactant Tween-80 on the rate of polyoma virus-induced cell transformation was studied on primary golden hamster embryo cultures. The investigations were made by means of a stereoscopic microscope after an incubation period of 14-15 days. Tween-80, in a concentration of 450-500  $\mu\text{g}/\text{ml}$ , enhanced the rate of *in vitro* transformation about tenfold compared to cultures without Tween-80. Incubation periods of seven and eight days following virus infection caused increases from 0.3 to 3.64% and from 1.3 to 7.7%, respectively, while no cell transformation was revealed after the same period in control cultures containing only Tween-80. The transformed cultures, both with and without Tween-80, were highly oncogenic. No change was found in the rate of transformation after one day of incubation in Tween-80, and reduced rate of transformation was revealed in cultures treated with Tween-80 prior to virus infection. After two weeks, the number of the transformation foci was ten times higher in cultures with Tween-80 than in those with polyoma only. The transformation enhancing effect of Tween-80 may be associated with its activating effect on DNA synthesis and mitosis.

- 1763 STUDIES ON THE STRUCTURE AND FORMATION OF POLYOMA DNA REPLICATIVE INTERMEDIATES. (E.) Meinke, W. (Scripps Clin. Fdn., La Jolla, Calif.) and D. A. Goldstein. *J Molec Biol* 61(3): 543-563, 1971.

Electron microscope (e.m.) observations on replicating polyoma virus revealed replicating DNA forms with two branch points and three branches. Isolation

these forms and analysis using pulse-labeling and density gradient centrifugation showed that a major portion of the replicating units sedimented as a heterogeneous 25S component. This component had a buoyant density the same as that of DNA from polyoma virus and it hybridized to polyoma viral DNA with the same efficiency as the reference supercoiled polyoma DNA. A fraction of the 25S DNA had stable forms. Equilibrium density gradient analysis and e.m. studies indicated that some of the 25S DNA existed as catenated dimers composed primarily of two open circular monomer subunits. Some, however, were monomers linked to supercoiled monomers. Open circular and supercoiled polyoma DNA dimers were also seen. A model was presented in an attempt to relate these observations to a mechanism of polyoma DNA replication.

- 1764 ULTRASTRUCTURAL AND IMMUNOLOGICAL STUDIES OF VIRAL PARTICLES ASSOCIATED WITH EPIDERMODYSPLASIA VERRUCIFORMIS. (It.) Pauluzzi, S. (Derm. Clin., Perugia U., Italy) and M. Binazzi. *Ann Ital Dermatol Clin Sperim* 24(2):152-160, 1970.

- 1765 DOUBLE-STRANDED  $f_2$  PHAGE RNA AS INTERFERON INDUCER. (E.) Doskocil, J. (Czechoslovak Acad. Sci., Prague), N. Fuchsberger, J. Vetrak, V. Lackovic and L. Borecky. *Acta Virol* 15:523, 1971.

- 1766 DETECTION OF POLYADENYLIC ACID SEQUENCES IN VIRAL AND EUKARYOTIC RNA. (E.) Sheldon, R. (Dept. Chem., U. Colorado, Boulder), C. Jurale and J. Kates. *Proc Nat Acad Sci USA* 69(2): 417-421, 1972.

- 1767 DETECTION AND ASSAY OF FELINE LEUKEMIA VIRUS (FeLV) BY A MIXED-CULTURE CYTOPATHOGENICITY METHOD. (E.) Rangan, S. R. S. (TRW Hazleton Lab., Vienna, Va.), P. P. Moyer, M. P. Cheong and E. M. Jensen. *Virology* 47(1):247-250, 1972.

- 1768 *IN VITRO* REASSEMBLY OF SHELL-LIKE PARTICLES FROM DISRUPTED POLYOMA VIRUS. (E.) Friedmann, T. (Inst. Biol. Stud., San Diego, Calif.) *Proc Nat Acad Sci USA* 68(10):2574-2578, 1971.

- 1769 ULTRACENTRIFUGATION STUDY OF MOUSE PLASMA CONTAINING RAUSCHER VIRUS. (E.) Mishra, L. C. (Sch. Pharmacy, St. U. New York, Buffalo) and P. Hebborn. *Life Sci* 10(23):1375-1380, 1971.

- 1770 SOME EFFECTS OF POLYETHYLENE IMINE ON THE DEVELOPMENT OF FRIEND VIRUS DISEASE IN MICE. (E.) Perlmutter, R. A. (Roswell Park Mem. Inst., Buffalo, N.Y.), and E. D. Holyoke. *J Med* 2(2):112-119, 1971.
- 1771 QUANTITATION OF IMMUNOGLOBULIN- AND VIRUS-PRODUCING CELLS IN RATS INFECTED WITH MOLONEY LEUKEMIA VIRUS. (E.) Cremer, N. E. (California State Dept. Pub. Hlth., Berkeley), D. O. N. Taylor and E. H. Lennette. *J Immun* 107(3):689-697, 1971.
- 1772 ENDONUCLEASIC ACTIVITY OF PURIFIED POLYOMA VIRUS PREPARATIONS. (Fr.) Cuzin, F. (Inst. Pasteur, Paris, France), D. Blangy and P. Rouget. *C R Acad Sci (Paris)* 273(25):2650-2653, 1971.
- 1773 SPECIAL VIRUS CANCER PROGRAM: TRAVAILS OF A BIOLOGICAL MOONSHOT. (E.) Anonymous. *Science* 174(4016):1306-1311, 1971.
- 1774 INCREASED INCIDENCE OF ROUS SARCOMAS IN RESPONSE TO EXCESS VITAMIN A. (E.) Polliack, A. (Hadassah U. Hosp., Jerusalem, Israel) and Z. Ben-Sasson. *Nature* 234(5331):547-548, 1971.
- 1775 ANTIGENIC RELATIONSHIP BETWEEN VARICELLA-HERPES ZOSTER AND HERPES SIMPLEX VIRUSES STUDIED BY THE GEL PRECIPITATION REACTION. (E.) Trlifajova, J. (Bulovka Hosp., Prague, Czechoslovakia), J. Sourek and M. Ryba. *Acta Virol* 15:293-300, 1971.
- 1776 IMMUNE COMPLEX DISEASES: I. PATHOLOGICAL CHANGES IN THE KIDNEYS OF BALB/c MICE NEONATALLY INFECTED WITH MOLONEY LEUKAEMOGENIC AND MURINE SARCOMA VIRUSES. (E.) Branca, M. (Clin. Res. Ctr., Harrow, England), S. DePetrìs, A. C. Allison, J. J. Harvey and M. S. Hirsch. *Clin Exp Immunol* 9:853-868, 1971.
- 1777 GROWTH OF NEWCASTLE DISEASE AND HERPES VIRUS AND INTERFERON PRODUCTION IN A MON-KEY-MOUSE HYBRID LINE. (E.) Coppey, J. (Curie Fdn., Paris, France). *J Gen Virol* 14(1):9-14, 1972.
- 1778 VIRUSES AND THE CONNECTIVE TISSUE DISEASES. (E.) Ziff, M. (U. Texas Southwestern Med. Sch., Dallas). *Ann Intern Med* 75:951-958, 1971.
- 1779 SEPARATION OF THE ENVELOPED AND UNENVELOPED HERPES SIMPLEX VIRUS PARTICLES. (E.) Matis, J. (Inst. Virol., Slovak Acad. Sci., Bratislava, Czechoslovakia), J. Lesso and F. Ciampor. *Acta Virol* 15(6):521, 1971.

## See also:

- \* (Rev): 1501, 1508
- \* (Viral): 1707
- \* (Immun): 1783, 1784, 1785, 1792, 1801, 1805, 1810, 1823, 1824, 1831, 1833, 1836, 1840, 1841, 1853, 1875



- 1780 GRAFT-*versus*-HOST REACTIONS AND THE VIRAL INDUCTION OF MOUSE LYMPHOMA. (E.) Hays, E. F. (Lab. Nuclear Med. Radiat. Biol., U. California, Los Angeles). *Cancer Res* 32(2):270-275, 1972.

An examination is reported of lymphoma development in hybrid mice undergoing graft-versus-host (GVH) reactions in a situation in which genetic predisposition to lymphoma development and the presence of murine leukemia virus (MuLV) were known to exist. Hybrid mice of strains CBA/H-T676 x AKRF<sub>1</sub> (TAF<sub>1</sub>) and SJL/J x AKRF<sub>1</sub> strains, all showing a high incidence of genetic susceptibility to lymphoma, were given inoculations with a preparation of MuLV cell-free filtrates of lymphomatous tissue. Attempts at producing a GVH reaction were carried out by subsequently injecting the animals with spleen cells taken from animals with and without previous exposure to MuLV. The parental spleen cells inoculated into hybrid mice did not elicit GVH reactions, however all mice did develop thymic lymphomas. Chromosome and tumor transfer studies were carried out on the tumor tissue confirming their host origin. Detailed analysis of results showed that lymphoma development was directly related to virus present in the inoculated splenic cells and not to a GVH reaction.

- 1781 LEUKAEMIA AND B.C.G.: A CONTROLLED TRIAL. (E.) Comstock, G. W. (Johns Hopkins U., Baltimore, Md.), V. T. Livesay and R. G. Webster. *Lancet* (7733):1062-1063, 1971.

Following a controlled trial of B.C.G. vaccination in a population of 64,126 persons, a distribution of 32 cases of leukemia, 15 cases of Hodgkin's disease, and 13 cases of lymphosarcoma were identified. All of the residents in a two county area were eligible for participation. The study population consisted of persons with tuberculin reactions read on the third day after intracutaneous injection of 0.1 µg P.P.D. Persons were classified as reactors or non-reactors to tuberculin. Non-reactors born in alternate years were vaccinated with B.C.G. and the remainder were left as controls. Over a period of 21 yrs, 60 persons were diagnosed as having developed leukemia, Hodgkin's disease or lymphosarcoma. The small number of cases identified from a large population after a long period of time was attributed to an inability to determine a complete count of cases. Follow-up was not carried out on cases which might have been seen at Federal and State hospitals. In addition, local hospital records were incomplete for the earlier years of the observation period. Losses in the population due to non-test related causes presented difficulties in data analysis. There was no indication in this experiment that B.C.G. vaccination had either prevented or encouraged the development of lymphosarcoma, leukemia or Hodgkin's disease.

- 1782 GENETIC CONTROL OF THE IMMUNE RESPONSE: A SELECTIVE DEFECT IN IMMUNOLOGIC (IgG) MEMORY IN NONRESPONDER MICE. (E.) Grumet, F. C. (Stanford U. Sch. Med., California). *J Exp Med* 135(1):110-125, 1972.

The kinetics of antibody formation after immunization with the synthetic polypeptide poly-L(Tyr,Glu)-poly-D, L-Ala--poly-L-Lys [(T,G)-A--L] in aqueous solution were studied in genetically high responder (H-2<sup>b</sup>) and non-responder (H-2<sup>K</sup>) inbred mice of strain C3H.SW. Both strains showed equally good primary responses consisting of rapid formation of IgM antibody during the first wk postimmunization. However, after booster injections on day seven (secondary antigen challenge) and day 30 (tertiary antigen challenge) post primary immunization, striking differences between responder and non-responder mice were seen. Responders rapidly developed high titers of IgG antibody, while non-responders produced almost none. Non-responder mice also failed to produce a significant increase in their IgM antibody after secondary and tertiary antigen challenge. Characterization of the antibody response on the basis of column chromatography and reactivity with specific antisera indicated that the antibodies belong to the IgM class of immunoglobulins. The data are consistent with the hypothesis that the immune response gene effect is exerted through thymus-derived cells which influence the conversion of antibody-producing, bone-marrow-derived B-cells from IgM to IgG production.

- 1783 IMMUNOBIOLOGICAL STUDIES OF TUMORS INDUCED BY MURINE SARCOMA VIRUS (KIRSTEN). (E.) McCoy, J. L. (Bionetics Res. Lab., Bethesda, Md.), A. Fefer, N. T. McCoy and W. H. Kirsten. *Cancer Res* 32(2):343-349, 1972.

Kirsten murine sarcoma virus (K-MSV) inoculated into C3H mice aged 3 days to 5 weeks induced tumors that grew progressively and metastasized or regressed. The incidence of tumors decreased with age, while the incidence of regression of palpable tumors increased. Similarly, preirradiation of the host increased the incidence of tumors and decreased the incidence of regressions. Some of the mice with local tumors that regressed died with internal sarcomas, but most died with erythroblastosis. Sera from mice with tumors that had regressed neutralized the oncogenic and focus-forming activities of K-MSV preparation but did not neutralize its ability to induce fatal erythroblastosis. The data suggest the immunological competence of the host can render it relatively resistant to *de novo* oncogenesis by K-MSV as well as to established autochthonous tumors. Two transplantable K-MSV-induced tumors (KS) grew progressively and killed adult syngeneic mice. The KS cells grew better and killed more pre-irradiated (43/49) than unirradiated (18/50) hosts. Mice immunized with lethally X-irradiated KS cells resisted challenge with viable KS cells. Fifty-two of 62 normal controls and 29 of 71 preimmunized mice developed fatal tumors. The results suggest that both transplantable tumors possess tumor-associated transplantation antigens. However, since the transplantable KS cells were also demonstrated to release oncogenic K-MSV, it could not be determined whether the transplantation antigens were cellular or virion.

- 1784 SURFACE ANTIGENS AND RELEASE OF VIRUS IN HYBRID CELLS PRODUCED BY THE FUSION OF A9 FIBROBLASTS WITH MOLONEY LYMPHOMA CELLS. (E.) Fényo, E. M. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), G. Grundner, G. Klein, E. Klein and H. Harris. *Exp Cell Res* 68(2):323-331, 1971.

Recently, two Moloney lymphoma lines from the same original tumor have been isolated, differing primarily in immunosensitivity and in the amount of viruses released. That is, the YAC lymphoma line contains the H-2<sup>a</sup> isoantigen complex, composed of H-2<sup>k</sup> and H-2<sup>d</sup> components, and fully expresses the Moloney-specific surface antigen; in addition, this line releases infectious virus particles. YACIR lymphoma line, on the other hand, does not release infectious virus particles; it does, however, contribute the same isoantigen complexes but at a lower concentration. In an attempt to discover whether these characteristics could be carried over into another cell, fusion of these two cell lines was performed with A9 mouse fibroblasts. These A9 cells are characterized by expression of the H-2<sup>k</sup> isoantigen complex, of the FMRGi (Friend-Moloney-Rauscher-Graffi) complex, and of the L antigen. When fusion was completed, as indicated by chromosomal markers, both YAC-A9 and YACIR-A9 hybrids had a fibroblastic morphology and growth pattern. The chromosome number took on the constitution of both parent cells; that is, the sum of the chromosome numbers in the parent cells approximately equaled the total number of chromosomes in the daughter cell. Also, in both YAC-A9 and YACIR-A9 cell hybrids, all of the surface antigens seen in the two parent cells were expressed as was proven by membrane immunofluorescence and mixed hemadsorption tests. It was shown by infectivity assay that the YACIR-A9 hybrid also did not release virus particles, while the hybrid cell YAC-A9 did. These findings suggest that the concentration of virus-induced surface antigen and the production of infectious virus vary independently.

- 1785 DIVERGENCE BETWEEN IMMUNOSUPPRESSION AND IMMUNOCOMPETENCE DURING VIRUS-INDUCED LEUKEMOGENESIS. (E.) Cerny, J. (Temple U. Med. Sch., Philadelphia, Pa.), R. F. McAlack, W. S. Ceglowski and H. Friedman. *Proc Nat Acad Sci USA* 68(8):1862-1865, 1971.

Four- to six-week-old BALB/c mice of both sexes were infected with Friend leukemia virus (FLV). The mice were immunized with either sheep erythrocytes or heat-killed *Vibrio cholerae*. As determined by the modified immunoplaque technique the primary antibody response to the bacteria was found to be slightly enhanced by the viral infection, whereas response to the erythrocytes resulted in 80% suppression in the number of anti-sheep cells. Earlier experiments indicated that the antigen-reactive cells to sheep erythrocytes were previously sensitized, while the anti-cholera antigen-reactive cells were not. Further studies involved immunizing the mice with the bacteria, infecting them with FLV and then challenging them with a second vaccine injection. The secondary response was markedly inhibited (90% suppression). Even though the number of plaque forming cells during the primary res-

ponse was not reduced, accumulation of cells in distant splenic foci was suppressed. The immune response appears to be susceptible to leukemia virus-induced immunosuppression only when there has been a previous stimulation of immunocytes by antigen. The experimental model of FLV infection provides a useful means for distinguishing between non-sensitized cells and memory-cell clones, and may be relevant to the problem of immunization of an individual against leukemia virus.

- 1786 ANTIGENIC CHANGES IN HUMAN BREAST NEOPLASIA. (E.) Edynak, E. M. (Nat'l. Conference Breast Cancer, Los Angeles, Calif.), M. P. Lardis and M. Vrana. *Cancer* 28(6):1457-1461, 1971.

A second fetal antigen of gamma mobility ( $\gamma$  fetal protein-2) has been found through Ouchterlony analysis. Antibody detecting this protein was found in serum of 6 of 2500 cancer patients but not in the serum of normal donors (0/229) nor in patients with non-neoplastic diseases (0/1562). The antibody was not restricted by sex or by tumor type. The antigen itself was not found in any of 35 normal adult surgical and autopsy tissue specimens, nor was it found in 30 diseased but non-neoplastic tissue specimens. However, antigen was detected in the breast cancers of 17 of 42 women undergoing radical mastectomy as well as in 18 of 35 specimens of breast tissue collected from apparently healthy tissue surrounding primary breast tumors. It is postulated that  $\gamma$  fetal protein-2 may be the product of a "primed" cell with malignant or near-malignant physiology found throughout the organ system. Such a phenomenon could then account for multifocal manifestations of concurrent or delayed manifestation in the contralateral breast.

- 1787 SOME ASPECTS OF THE IMMUNE DEFENSE AGAINST CANCER: I. *IN VITRO* STUDIES ON ANIMAL TUMORS. (E.) Hellström, K. E. (U. Washington Med. Sch., Seattle,) and I. Hellström. *Cancer* 28(5):1266-1268, 1971.

Literature and the authors' previous work on *in vitro* tumor immunology are reviewed to elucidate mechanisms of immune defense against cancer. Tissue culture assays were used to detect lymphocyte-mediated immunity to specific antigens from humans and experimental animals by observing plating efficiency or destruction of target cells. The degree of immunity was similar in animals with or without progressively growing tumors. Serum "blocking factors" were present in animals with growing tumors which prevented the lymphocyte-mediated immune response. This blocking effect was found to be specific for tumor type and was shown to be effective *in vivo*. Blocking serum enhanced the growth of tumors *in vivo*. Tumor removal and/or splenectomy decreased the blocking effect. Subsequently, "unblocking" factors were found which could reverse the "blocking" effect and permit an immune response. Inoculation with "unblocking" sera caused tumor regression in mice. Lymphocyte-mediated immunity, "blocking, and



"unblocking" could be detected by both the microcytotoxicity assay and macrophage migration technique.

- 1788 IMMUNOLOGIC COMPETENCE OF REGIONAL LYMPH NODES IN PATIENTS WITH MAMMARY CANCER. (E.) Humphrey, L. J. (Emory U. Sch. Med., Atlanta, Ga.), C. Barker, C. Bokesch, D. Fetter, J. R. Amerson and O. R. Boehm. *Ann Surg* 174(3):383-391, 1971.

Female C3H/HeHa mice with transplanted methylcholanthrene sarcoma (MC-Sa) were used in an immunological study to determine the location of tumor immunity in tumor bearing animals. In addition, a study was made of patients with breast disease to determine the immunologic competence of their regional lymph nodes. The results of the syngenic mouse strain study indicated that the tumor specific immunity resides predominantly in the spleen with only traces in the regional lymph nodes. Studies on patients with benign breast disease indicated a good response to injection of tetanus toxoid. Patients with mammary cancer, irrespective of whether the regional lymph nodes were removed or left intact, did not respond to ipsilateral injections of tetanus toxoid. These results indicated immunological incompetence of the regional nodes. The results in patients treated by radical mastectomy also indicated incompetence of the regional nodes but the remainder of the immune system was functioning. In patients treated by radical mastectomy it was shown that those with antibody in the first serum sample could produce a secondary immune response and that the majority of the patients' lymph node cells did not produce antitoxoid antibody *in vitro* in the presence of serum antibody. Two patients developed anti-breast cancer antibody after removal of the primary growth and axillary nodes.

- 1789 HL-A AND THE GROUP FIVE SYSTEM IN HODGKIN'S DISEASE. (E.) van Rood, J. J. (U. Hosp., Leiden, Netherlands) and A. van Leeuwen. *Transplantation Proc* 3(3):1283-1286, 1971.

Ninety-eight patients with Hodgkin's disease were typed for HL-A and for antigens of the other defined tissue antigen system, the Group Five System. The leukocyte typing was performed by: 1) the one stage microcytotoxicity test for most of the HL-A antigens; 2) micro-EDTA-agglutination test for some of the HL-A antigens; 3) the two stage microtoxicity method for the antigen R\* (W 5); and; 4) the van Rood, Leeuwen and Zweerus histocompatibility test for antigens 5a and 5b. There was found to be a significant increase of R\* (W 5), the incidence of the 4a was decreased, and the presence of antigen 5a was increased.

- 1790 DIRECT PLAQUE-FORMING CELL RESPONSE TO SHEEP RED BLOOD CELLS IN RAT SPLEEN UNDERGOING GRAFT-VERSUS-HOST REACTION. (E.) Medzihradsky,

J. (Slovak Acad. Sci., Bratislava, Czechoslovakia) and L. Novotna. *Neoplasma* 19(1):19-25, 1972.

Hemolytic plaque-forming cell (PFC) response to sheep red blood cells (SRBC) in the spleen of F<sub>1</sub> hybrid rats grafted with parental spleen was examined. The data showed that animals altered by the graft-versus-host reactions (GVHR) 10 to 22 days following parental spleen grafting demonstrated a lower frequency of PFC/10<sup>6</sup> spleen cells than did litter mates without GVHR. The number of PFC/spleen in these animals was depressed only when no enlargement or minor enlargement of the tested spleen due to GVHR was found. However, in animals with markedly enlarged spleen, normal or increased PFC/spleen response was shown. Enhanced PFC depression was demonstrated when i.p. GVHR induction and sensitization with SRBC performed at the same site. Insignificant decrease of PFC/10<sup>6</sup> spleen cell counts was caused by high doses of syngeneic spleen grafted i.p. Hemagglutinin titers follow the PFC/spleen response with markedly significant reduction of titer ( $P < 0.001$  with both controls) in animals in the low spleen weight group. The data are discussed with reference to the possibility of immunity restoration by host-type cell proliferation during GVHR.

- 1791 STIMULATION OF DNA AND PROTEIN SYNTHESIS IN FETAL-RAT LIVER CELLS BY SERUM FROM PARTIALLY HEPATECTOMIZED RATS. (E.) Paul, D. (Salk Inst. Biol. Stud., San Diego, Calif.), H. Leffert, G. Sato and R. W. Holley. *Proc Nat Acad Sci USA* 69(2):374-377, 1972.

The stimulation of DNA and protein synthesis by medium containing dialyzed serum obtained from male Fischer 344 rats which were either partially hepatectomized or sham-operated was studied in confluent primary fetal rat liver cells by incorporation of <sup>3</sup>H-thymidine or <sup>3</sup>H-leucine. Precursor incorporation studies were begun five days after plating 4 x 10<sup>5</sup> cells using arginine-deficient medium supplemented with 10% dialyzed serum obtained from rats six hours after the operation. Fetal liver cells exposed to serum from partially hepatectomized rats showed enhanced stimulation of both DNA and protein synthesis in 24 hour pulse-label experiments, as compared with cultures incubated in sera from normal or sham-operated rats. 3T3 mouse fibroblasts did not respond to serum from partially hepatectomized rats as compared to normal serum. The rate of DNA synthesis in cultured fetal liver cells increased markedly about 16 hours after incubation in serum from partially hepatectomized rats; in contrast, the rate of DNA synthesis in cultures exposed to normal serum was slower and reached a value only 75% of that of the former. The time course of the rate of DNA synthesis in fetal liver cells after addition of normal rat or partially hepatectomized rat serum was similar to that observed in a liver remnant *in vivo* after partial hepatectomy. Increasing the concentration of dialyzed serum in the culture medium increased both DNA and protein synthesis as determined by incorporation of labeled precursor (maximum serum concentration tested was 50%). These results suggest that DNA synthesis in fetal liver may be regulated by a positive control system mediated by serum factors.

- 1792 PRESENCE OF GROUP-SPECIFIC ANTIGEN OF AVIAN SARCOMA LEUKOSIS COMPLEX IN SUBCELLULAR FRACTIONS OF TUMOURS INDUCED BY SCHMIDT-RUPPIN STRAIN OF ROUS SARCOMA VIRUS. (E.) Sovova, V. (Czechoslovak Acad. Sci., Prague), O. Mach and J. Kara. *Folia Biologica* 17(5):304-311, 1971.

The Gs antigen is known to be an internal component of the virus particle and is located in the cytoplasm of tumor cells, frequently in the form of granules. The present study seeks to determine whether these Gs antigens are bound to some subcellular particles in the cytoplasm or whether they exist in the free state. Rat tumor cells (XC) and hamster tumor cells (RSH-mix) were chosen for analysis. Both these transformed lines are virogenic: they yield infectious Rous sarcoma virus particles *in vitro* and *in vivo* after interaction with chicken cells carrying the Schmidt-Ruppin strain of Rous sarcoma virus. The RSH-mix cells were first homogenized and then subjected to complement fixation studies. It was found that Gs antigen was present not only in the soluble fractions of the cell homogenate but also in the fraction containing endoplasmic reticular membranes and mitochondrial isolates. Corroboration of this data was obtained when analysis of the XC cells yielded the same evidence. The Ouchterlony method of immunoprecipitation in agar was then used to detect the complexity and possible qualitative differences in the Gs antigen. It was discovered that the Gs antigen in the XC cells is not antigenically homogeneous since it was found that there are at least four components present.

- 1793 EFFECTS OF A COUPLED TUMOR PROTEIN ANTIGEN (LEWIS CTPA) ON THE GROWTH OF TRANSPLANTED TUMORS IN INBRED MICE. (E.) Phillip, M. J. (Dept. Biol., John Carrol U., U. Heights, O.), A. J. Lewis and N. H. Daily. *Oncology* 25(6):528-535, 1971.

The effects of coupled tumor protein antigen (Lewis CTPA) on the growth of transplanted tumors in inbred mice is discussed. A spontaneous adenocarcinoma obtained from a C<sub>3</sub>H/HeJ mouse was implanted in 125 male and female 13-wk-old C<sub>3</sub>H/HeJ mice. Mice were then given weekly injections of a tumor protein antigen prepared by coupling the antigen from spontaneous mouse tumors to human  $\alpha$ -globulin with bis-diazotized benzidine. Weekly examination of the tumors showed that the incidence of observable tumor in the untreated control mice was much higher throughout the six-wk test period than that in mice receiving the CTPA. At the end of the experiment the tumor incidence in CTPA-treated mice was 86.7% in contrast to 100% in the untreated group.

- 1794 TRANSIENCE OF IMMUNE RESPONSES TO TUMOUR ANTIGENS IN MAN. (E.) Odili, J. L. (Roy. Infirm., Manchester, England) and G. Taylor. *Brit Med J* (5787):584-586, 1971.

An examination was made of serial serum samples from 36 patients undergoing surgical removal of malignant tumors. Five patients showed tumor-specific anti-

body responses; in four of these five, the autologous sera reacted against the nuclear fraction of the tumors and the fifth reacted against the microsomal fraction. Using complement fixation tests the antibodies were shown to be strictly tumor-specific. The findings suggest that the *in vivo* reaction between tumor neoantigens and tumor antibodies may be one reason for the low frequency of tumor antibody detection.

- 1795 LYMPHOCYTE TRANSFORMATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA. (E.) Jones, L. H. (Hosp. Sick Children, London, England), R. M. Hardisty, D. G. Wells and H. E. M. Kay. *Brit Med J* 4(5783):329-330, 1971.

Natural or artificially enhanced immune reactions may play a part in the response to treatment of acute lymphoblastic leukemia. Since lymphocyte involvement is probable it is important to determine the defects in lymphocyte function, the effect of treatment including immunotherapy and the length of remission as related to lymphocyte reactivity. A group of 40 patients with acute lymphoblastic leukemia was studied; 22 patients received immunotherapy designed to compare the efficiency of B.C.G. and methotrexate. During a period of five months they received prednisolone, vincristine, mercaptopurine and L-asparaginase. The remaining 18 patients received similar chemotherapy but without L-asparaginase. Blood samples were taken eight days following a dose of B.C.G. and three days following administration of methotrexate. Lymphocytes were separated by simple settling of cells and polymorphs were removed by using iron carbonyl and methyl cellulose. The cells were then cultured for 72 hr with phytohemagglutinin, and the transformation of lymphocytes by phytohemagglutinin was tested. The degree of transformation was assayed by the uptake of tritiated thymidine as measured by liquid scintillation counting. Control cultures of lymphocytes from healthy adults were run in parallel with each of the test cultures. No significant differences were found in the results of tests on lymphocytes from patients treated with B.C.G. and those from patients given methotrexate, nor was any difference detected between patients and controls. No evidence of any systematic change in lymphocyte responsiveness during a remission was detected.

- 1796 IMMUNOLOGIC RESPONSE IN PATIENTS TO CELLS OF THEIR OWN TUMOR. (E.) Albert, Z. (Polish Acad. Sci., Wroclaw), A. Harlozinska, R. Richter, J. Salwa and Z. Singer. *Arch Immun Ther Exp* 19(4):455-463, 1971.

This study was conducted to determine whether the blood serum of cancer patients contained specific antitumor antibodies. Thirty-two patients suffering from epithelial tumors and 22 patients with hematopoietic-derived neoplastic diseases were subjected to blood serum analysis by the indirect immunofluorescence technique. It was found that eight of the patients suffering from epithelial tumors (24%) and eight of the patients with hematopoietic neoplasms



(36%) exhibited antitumor autoantibodies. The immunity observed indicated that specific transplantation tumor antigens were localized on the surface of the tumor cells. Interestingly, it was found that control individuals who were free of cancer all gave negative antibody results when tested. These results indicate the existence of specific tumor antigens, at least in some human tumors, and support the possibility of endogenous host defense against developing neoplasms.

- 1797 HEPATITIS-ASSOCIATED ANTIGEN AND HEPATOCELLULAR CARCINOMA IN TAIWAN. (E.) Tong, M. J. (U.S. Naval Med. Res. No. 2, Taipei, Taiwan), S.-C. Sun, B. T. Schaeffer, N.-K. Chang, K.-J. Lo and R. L. Peters. *Ann Intern Med* 75(5):687-691, 1971.

The prevalence of "hepatitis-associated antigen" (HAA) in patients with primary hepatocellular carcinoma is investigated. The study was performed on Taiwan, a population which is known to experience a high incidence of liver disease, particularly in males. Fifty-five patients with hepatocellular carcinoma (52 men and three women) and 943 healthy control individuals were tested for HAA titers by polyacrylamide gel electrophoresis and for alpha fetoglobulin levels by the agar double diffusion technique. It was found that HAA was present in 80% of the patients with hepatocellular carcinoma and that alpha fetoglobulins were present in 58%. Of the 55 patients with hepatocellular carcinoma, 32 had demonstrable alpha fetoglobulin in their blood serum, and of these 25 (78%) had detectable HAA. Of the 23 patients with hepatic carcinoma and negative alpha fetoglobulins, 19 had demonstrable antigen in their sera (83%). However, in the controls, HAA was shown in only 14%, while the alpha fetoglobulins were not present at all. Therefore, the finding of a highly positive correlation suggests a significant relationship between viral hepatitis and hepatocellular carcinoma, at least among residents of Taiwan.

- 1798 PREPARATION OF A "CHEMICAL VACCINE" AGAINST TUMOR PROGRESSION. (E.) Shier, W. T. (Salk Inst., San Diego, Calif.) *Proc Nat Sci USA* 68(9):2078-2082, 1971.

This paper describes a synthetic antigen designed to elicit an immune response able to crossreact with the wheat-germ agglutinin (WGA) receptor site on tumor cells. A poly(L-aspartic acid) molecule having some free carboxyl groups substituted with a sugar moiety was mixed with ethylenediamine to form antigen A. Agar diffusion assay was then performed to determine whether the antigen A had a specific affinity for the WGA receptor site. When A was found specific for the WGA site, it was complexed with methylated bovine serum albumin (MBSA) and tested as an immunizing agent *in vivo*. It was discovered that the complex A(MBSA) could inhibit the growth of myelomas induced in BALB/c mice by the transformed lines XS63.5 and MOPC 70A; five times as many transplanted myeloma tu-

mor cells were rejected as were rejected by identically treated controls. Complexed A antigen could delay the formation of tumors induced by 3-methylcholanthrene. Although affecting tumor growth this immunization did not impair normal cell growth. In addition, it was determined that the observed protection was mediated by specific action of the immune system. Protection could be transferred from donor to unimmunized mice via spleen cells, while only some protective enhancement was transferred with serum.

- 1799 RESISTANCE TO MURINE TUMORS CONFERRED BY CHRONIC INFECTION WITH INTRACELLULAR PROTOZOA, *Toxoplasma gondii* AND *Besnoitia jellisoni*. (E.) Hibbs, J. B., Jr. (Stanford U. Sch. Med., California), L. H. Lambert, Jr. and J. S. Remington. *J Infect Dis* 124(6):587-592, 1971.

The obligate intracellular protozoans *Toxoplasma gondii* and *Besnoitia jellisoni* were injected i.p. into female mice of the Swiss-Webster strain, male and female DBA/2 mice, female strain AKR mice, and into retired breeders of the C<sub>3</sub>H/He strain. These mice were then challenged with the protozoans to test immunity and were either watched for the development of spontaneous cancer or subjected to ascites injections of sarcoma or leukemia cells. It was found that increased resistance was induced to both autochthonous and transplantable neoplasms in mice that had been immunized with the protozoans. Resistance was marked against spontaneous mammary tumor in C<sub>3</sub>H/He mice, against induced AKR leukemia, against Friend leukemia, and against induced sarcoma-180; resistance was present but not impressive in mice injected with leukemia-1210 cells. It is suggested that an epidemiologic study be done to correlate natural infection with *Toxoplasma* and subsequent tumor development.

- 1800 EFFECT OF RNA EXTRACTED FROM A NEOPLASTIC CELL LINE ON LYMPHOCYTE CULTURES. (E.) Giraudo Conesa, L. C. (Natl. Acad. Med., Buenos Aires, Argentina), M. E. M. Colmerauer, A. E. Bachmann and A. Pavlovsky. *Acta Haemat* 46(1):45-49, 1971.

It has been shown that addition of RNA to lymphocyte cultures will inhibit blastic transformation. To study this further, RNA was first extracted from a cell culture line derived from a patient with a lymphosarcoma. The RNA was purified and then added in various concentrations to experimental lymphocyte cultures from both normal donors and the patient. Concurrently, control lymphocyte cultures received no RNA exposure. Both control and experimental groups were incubated, and on the third, seventh, and 14th days, slide preparations were made using May-Grunwald-Giemsa, periodic acid Schiff (PAS), and acridine orange stains. It was found that when lower and intermediate doses of RNA were added the normal lymphocyte cultures showed no significant differences in blast percentage compared to the respective control group. However, higher doses caused

a lower blast value. In the cells derived from the lymphosarcoma patient, the highest initial percentage of blast transformation was observed on the third day with the intermediate doses of RNA, but this reaction disappeared by the seventh day. The effects of lower and higher doses of the RNA appeared mainly on the 14th day of culture. In the former there was a stimulation of transformation, while in the latter there was inhibition. All values, it should be noted, differed significantly from the control. Therefore, it can be concluded that exogenous RNA interferes with the biologic function of the lymphocyte either by stimulating or inhibiting its transformation, and that both effects can be correlated with the amount of RNA added.

1801 *IN VITRO* IMMUNE RESPONSES OF SPLEEN CELLS FROM FRIEND VIRUS INFECTED MICE. (E.)

Dracott, B. N. (Roy. Coll. Surg. England, London), N. Wedderburn and M. H. Salaman. *J Gen Virol* 14(1):77-86, 1972.

BALB/c mice were inoculated with Friend leukemia virus (FLV) and injected after an interval with sheep erythrocytes. Over a five day period, mice were sacrificed and subjected to splenectomies. The cells of the spleens were harvested, and the cells were separated into macrophage-like (M) and lymphocyte-like (L) cells and cultured for hemolytic plaque assays. After three days of virus infection the primary immune response was depressed and after four days it was down to 11% of normal values. The immune defect was only present in the L cell fraction.

1802 IMMUNOFLUORESCENCE STUDIES ON SERA OF PATIENTS WITH BREAST CARCINOMA. (E.)

Priori, E. S. (U. Texas M. D. Anderson Hosp. Houston), G. Seman, L. Dmochowski, H. S. Gallager and D. E. Anderson. *Cancer* 28(6):1426-1471, 1971.

Primary cell cultures were initiated from patients suffering with breast cancer, fibrocystic disease and osteosarcoma. These cultures plus blood sera obtained from 46 patients with carcinoma were subjected to indirect immunofluorescence studies using fluorescein-conjugated goat antihuman globulin. Sera from 45 blood bank donors was treated in the same manner and used as a control. In 60% of the cases the fluorescence reaction was centered around perinuclear and cytoplasmic areas of the cells and was not associated with age, blood type or transfusion history, number of children conceived, type of treatment administered, familial history, or presence or absence of metastases. However, the intensity of the reaction was found to decrease over a period of three to five years post-surgery. Absorption studies on the blood sera of patients suffering from breast cancer, fibrocystic disease, and osteosarcoma also indicated that the three diseases may have a common tumor antigen, unrelated to Forssman or heterophile antibodies.

1803 PHENOMENON OF ENHANCEMENT ASSOCIATED WITH MURINE LEUKEMIA. (E.) Rumi, L.

(Nat'l. Acad. Med., Buenos Aires, Argentina), M. E. M. Colmerauer, R. C. Braylan, C. D. Pasqualini and S. L. Rabasa. *Medicina* 31(5):372-376, 1971.

Inbred BALB mice of both sexes and from 2 to 3 months of age were subjected to i.p. injections of L423 spontaneous leukemic cells, L142 induced leukemic cells, H222 or H110 induced human leukemic cells, or L370 from S180 immune mice. Dilutions were of 5, 10, 20, 50, 100, or 200 cells. The median lethal dose was calculated for each leukemic line; this ranged from 14 to 132 cells. Challenge with homologous cells was performed on mice surviving the first injection. It was found that, after a period of latency, a typical enhanced leukemic growth developed. This growth was characterized by large bilateral masses around the dorsal regions of the forelimbs and hindlimbs. Such masses, when transplanted syngeneically as cellular or acellular passages gave rise to disseminated leukemias, containing a large number of intracisternal A particles. It is concluded that subthreshold doses of syngeneic leukemic cells suppress the immunological reaction of the host to later challenges, thus causing tumor growth in an unusually aggressive manner.

1804 HL-A GENOTYPE OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA. (E.) Singal, D.

P. (Dept. Surg., McMaster U., Hamilton, Ontario, Canada), N. Naipaul, R. Berry, M. K. Pai and A. Zipursky. *Humangenetik* 13(3):234-237, 1971.

A genetic study of ten patients with acute lymphoblastic leukemia is reported. All were typed for 21 HL-A specificities. Family analyses were used to determine the genotype of nine patients. All patients had different HL-A phenotypes; HL-A2 occurred in five patients, HL-A1 in four patients, and HL-A8 in four patients. Haplotype HL-A1,8 occurred in five of 18 instances. A slight increase in the incidence of antigens HL-A1 and HL-A8 was discovered phenotypically. The HL-A antigens present on cells of the leukemia patients were in accordance with the expectations from the family analyses. Thus, no loss of the HL-A antigens on lymphocytes could be detected in the present series.

1805 TYPE 12 ADENOVIRUS PROTEINS: INFLUENCE ON TUMOR DEVELOPMENT IN OFFSPRING OF IMMUNIZED PREGNANT HAMSTERS. (E.) Dreesman, G. R. (St. Louis U. Sch. Med., Mo.) H. Pinkerton, E. S. Holtwick and J. R. Suriano. *Proc Soc Exp Biol Med* 137(4):1337-1342, 1971.

The effectiveness of maternal immunization with purified protein components of adenovirus 12 (Ad 12) in repressing the development of Ad 12 oncogenesis in newborn hamsters is reported. Ad 12 was purified from infected KB (human) cells by sonic disruption and centrifugation and hexon and core proteins were isolated from supernatants. Pregnant hamsters were



immunized with hexon, core protein, or purified Ad 12 on the third and 10th days of pregnancy; virion and virus protein preparations were emulsified in Freund's complete adjuvant. Control pregnant hamsters were injected with phosphate-buffered saline emulsified in the adjuvant. Offspring of treated and control hamsters were challenged with  $4 \times 10^5$  plaque-forming units of Ad 12 within 12 hr of birth. All maternally immunized hamsters responded with low but significant serum antibody titer against the group-specific virion antigens. By 5 wk postinoculation, 55% of control offspring developed s.c. tumors. Immunization of mothers with purified virion and hexon provided obvious protection to offspring; only 6% of offspring of virion-immunized mothers and 12% of offspring of hexon-immunized mothers developed palpable tumors by 5 wk. Neither core protein nor Freund's adjuvant provided significant protection. By 65 days after Ad 12 challenge, the average tumor wt in adjuvant controls was 8.9 g, compared with average tumor wts of 2.5 and 3.1 g in hamsters immunized with purified virion and hexon, resp. The findings support the conclusion that maternal immunization with hexon and purified virion results in the inhibition of growth of primary tumors induced by Ad 12.

- 1806 SYNTHESIS, ASSEMBLY, AND SECRETION OF GAMMA GLOBULIN BY MOUSE MYELOMA CELLS: III. ASSEMBLY OF THE THREE SUBCLASSES OF IgG. (E.) Baumal, R. (Albert Einstein Coll. Med., Bronx, N.Y.), M. Potter and M. D. Scharff. *J Exp Med* 134(5):1316-1334. 1971.

Cultured cells derived from fourteen myeloma tumors, cells from two previously established myeloma cell lines, and cells from the popliteal lymph nodes of immunized BALB/c mice were studied to determine synthesis, assembly and secretion of the three major subclasses of mouse IgG. Of the cytoplasmic proteins produced in a 15-min period, 15 to 43% were IgG. The major precursors of IgG<sub>2a</sub> and IgG were H<sub>2</sub> and H<sub>2</sub>L, with HL as an intermediate in all tumors examined. However, the precursor of IgG<sub>2b</sub> was HL. Assembly of the covalent and noncovalent IgG was seen following release of H and L chains, with the assembly completed between 10 and 30 min after synthesis of the polypeptide chains.

- 1807 HL-A ANTIGENS IN HAEMATOLOGICAL MALIGNANT DISEASES. (E.) Jeannet, M. (U. Hosp., Geneva, Switzerland) and C. Magnin. *Europ J Clin Invest* 2(1):39-42, 1971.

An immunologic study of 170 patients with hematologic malignant diseases was made to determine whether an association exists between blood group antigens and blood malignancies. HL-A 11 was absent in many of the patients with hematologic malignant diseases. Other findings were increased frequency of: 1) HL-A 1 in chronic myelocytic leukemia; 2) HL-A 2 in acute myeloblastic leukemia; 3) W 28 in lymphomas; and 4) W 15 in Hodgkin's disease. The number of subjects studied was insufficient for results to be statistic-

ally significant, but the existence of a correlation between HL-A antigens and hematologic malignant diseases was suggested.

- 1808 DETECTION OF HUMAN AND CHICK NUCLEAR ANTIGENS IN NUCLEI OF CHICK ERYTHROCYTES DURING REACTIVATION IN HETEROKARYONS WITH HeLa CELLS. (E.) Ringertz, N. R. (Med. Nobel. Inst., Karolinska Inst., Stockholm, Sweden), S.-A. Carlsson, T. Ege and L. Bolund. *Proc Nat Acad Sci USA* 68(12):3228-3232, 1971.

Inactive chick erythrocytes fused with HeLa cells using inactivated Sendai virus resumed RNA synthesis and underwent nuclear enlargement. The distribution of human nucleoplasmic and nucleolar antigens using antinuclear and antinucleolar antibodies from patients with various autoimmune diseases was studied to determine if this activation was dependent upon utilization of HeLa proteins. The indirect immunofluorescence technique revealed a gradual increase in human nucleolar and nucleoplasmic material in chick nuclei over a 42-hr period after fusion. No human cytoplasmic antigens were detected in chick nuclei. Newly-formed chick nucleoli gave a positive reaction for both human- and chick-specific antinucleolar antibodies with the reaction to human antibody appearing first. A reaction to human antinucleoplasm serum was also seen with 20% of fused chick nuclei 28 hr after cell fusion; however, close to 100% of these nuclei gave a positive reaction with the human specific antinucleolar antibodies. HeLa nuclei reacted with human antinuclear sera to the same extent in heterokaryons and mononucleated, unfused cells. Fused HeLa nucleoli gradually increased in reactivity with chick-specific antinucleolar antibodies after fusion. By 76 hr after fusion some mononucleated large cells resembling HeLa cells also reacted with chick-specific antinucleolar antibodies, suggesting the possible formation of human-chick synkaryons. The results suggest that human nuclear proteins play an important part in the reactivation of the chick genome.

- 1809 SYNTHESIS AND SECRETION OF IgE BY AN ESTABLISHED HUMAN MYELOMA CELL LINE. (E.) Nilsson, K. (Wallenberg Lab., U. Uppsala, Sweden) *Clin Exp Immunol* 9:785-793, 1971.

The rate of IgE production *in vitro* and the cell population proliferation rate by the established human myeloma line 266B1 have been studied quantitatively under various tissue culture conditions. The rate of extracellular IgE accumulation varied according to the type of tissue culture media used, the period of time elapsed after explantation and the cell density. The maximum production rate of  $8.1 \times 10^{-12}$  g IgE/cell/48 hr was noticed at cell densities  $<10^6/30$  ml and with the presence of feeder human skin fibroblasts or glia-like cells or with the use of conditioned media harvested from such cells. IgE production was highest when the cells were in their best physiological condition as measured by the rate of cell proliferation.

A marked stability in the rate of synthesis of IgE was noted over a one year period. The 266 B1 cell line is the only human myeloma line thus far reported, which continuously produces complete immunoglobulin molecules *in vitro* identical to those manufactured *in vivo*.

1810 INHIBITION OR ENHANCEMENT OF IMMUNOLOGICAL INJURY OF VIRUS-INFECTED CELLS. (E.)

Brier, A. M. (Natl. Inst. Dental Res., Natl. Inst. Hlth., Bethesda, Md.), C. Wohlenberg, J. Rosenthal, M. Mage and A. L. Notkins. *Proc Nat Acad Sci USA* 68(12):3073-3077, 1971.

HeLa, WI-38 and primary rabbit kidney cells were infected with herpes simplex, vaccinia, influenza, or Newcastle disease virus. Within hours after infection, new antigens appeared on the surface of infected cells. The interaction of specific antiviral antibody and complement with these antigens resulted in cell destruction, which was quantitated by the release of  $^{51}\text{Cr}$ . A number of factors can influence the degree of immunological injury, including the density of viral antigens on the surface of infected cells, the nature of the antiviral immunoglobulin, and the presence of anti-immunoglobulins. Immunologically mediated destruction of virus-infected cells may serve as a defense mechanism against certain viral infections and alternately may contribute to the disease of the host.

1811 QUANTITATION OF THE CELL-MEDIATED IMMUNE RESPONSE: I. THE NUMBER OF CYTOLYTICALLY ACTIVE MOUSE LYMPHOID CELLS INDUCED BY IMMUNIZATION WITH ALLOGENEIC MASTOCYTOMA CELLS. (E.) Henney, C. S. (Dept. Med., Johns Hopkins U., Baltimore Md.). *J Immunol* 107(6):1558-1566, 1971.

Quantitative aspects of the cell-mediated immune response of C57BL mice to a mouse DBA/2 mastocytoma cell have been studied by an *in vitro* assay involving the cytolytic activity of splenic lymphocytes towards  $^{51}\text{Cr}$  labeled target cells. Cytolysis of the DBA/2 mastocytoma cells by "sensitized" C57BL lymphocytes was shown to be a "one-hit" phenomenon, i.e., that lysis of a target cell resulted from a single interaction with specifically sensitized "effector" cells. Kinetic studies showed that the rate of target cell destruction fell markedly with time following mixing with lymphocytes, and thus suggested that there is reciprocal death of the interacting cells. The number of effector lymphocytes in the splenic pool of sensitized animals was calculated by determining the maximal number of target cells that a given number of lymphocytes could lyse under specified conditions in gross target cell excess. Such determinations were used to compare the effect of mode and dose of antigenic stimulation on the cell-mediated immune response. Optimal antigenic stimulation of C57BL mice with alloantigenic mastocytoma cells was found to be by the i.p. route. Maximal responses were elicited with  $10^7$  cells and occurred 11 days following antigenic stimulation. Under these conditions it was esti-

mated that approximately 4% ( $4 \times 10^4$  out of  $10^6$ ) of the lymphocytes were effector cells. Incorporation of the mastocytoma cells in adjuvants (either complete or incomplete Freund's) resulted in a marked diminution of both humoral and cell mediated immune responses. Using complete Freund's adjuvant the maximal number of effector cells produced following antigenic stimulation with  $3 \times 10^7$  mastocytoma cells was approximately  $5 \times 10^3/10^6$  lymphocytes. The number of effector lymphocytes resulting from stimulation with  $3 \times 10^7$  mastocytoma cells rose exponentially from day 4 (when the cytolytic activity was first demonstrable) and when there were calculated to be 50 effectors/ $10^6$  lymphocytes to day 11 ( $4 \times 10^4/10^6$  lymphocytes) and fell thereafter. The generation time of the cell population involved in cytotoxicity was estimated to be approximately 17 hr.

1812 STUDIES ON THE ETIOLOGY OF TROPHOBLASTIC TUMORS: I. CLINICAL OBSERVATION: THE ANALYSIS OF HOST CONDITIONS. (Jap.) Nishio, Y. (Gifu U. Sch. Med., Japan). *Acta Sch Med Univ Gifu* 18(4):420-438, 1970.

A study of 105 cases of trophoblastic tumor was conducted between 1959 and 1969 at the Gifu University Hospital, Japan. During this period, the total number of pregnancies was 2312, and the frequency of trophoblastic tumor was 45.5/1,000, of which hydatidiform mole cases were 11.24; unknown forms, 16.43; invasive mole, 9.08; and chorionepithelioma 8.65. Ages ranged from 16 to 51, but the highest number of cases was found in women in their twenties when most pregnancies occurred. In examining the ratio of pregnancy and occurrence of trophoblastic tumor, the ratio per 100 pregnancies was 11.11 among teenagers, 7.76 in women in their twenties, 2.17 in those in their thirties, and 17.86 in those in their forties. The occurrence of trophoblastic tumors, especially hydatidiform mole, was found more frequently among women in their twenties and forties than those in their thirties. More than 50% of invasive mole (11 cases) and 40% of chorionepithelioma (eight cases) occurred in women above 40. Among 41 cases of invasive mole and chorionepithelioma, 25 were preceded by hydatidiform mole; that is, hydatidiform mole in women over the age 40 showed a high tendency for developing into invasive mole or chorionepithelioma. The occurrence of hydatidiform mole among women over age 40 was often preceded by a long period of nonpregnancy (5-18 yr, average 10 yr). Forty-four percent of hydatidiform mole cases occurred in the first pregnancy, 47% in the first to third pregnancies, and 9% occurred in women who were pregnant more than 5 times. Invasive mole and chorionepithelioma developed in women who were pregnant 4.5 to 5.4 times.

1813 ASSOCIATION OF H-2 TYPES WITH GENETIC CONTROL OF IMMUNE RESPONSIVENESS TO IgA ALLOTYPES IN THE MOUSE. (E.) Lieberman, R. (Natl. Inst. Allergy Infect. Dis., Natl. Inst. Hlth., Bethesda, Md.) and W. Humphrey, Jr. *Proc Nat Acad Sci USA* 68(10):2510-2513, 1971.



The immune response to BALB/c IgA myeloma proteins (Ir-IgA) in inbred strains of mice of various H-2 types was studied. Mice from five different linkage groups were immunized with IgA myeloma proteins, which carry allotypic determinants A on their heavy-chain constant region ( $C_H$ ) and myeloma specific or idiotypic determinants on their Fab region. Four s.c. protein injections distributed over six sites were given. Following immunization, the mice were bled twice weekly to obtain antisera. Antibody assays included double diffusion agar gel plate analyses and passive hemagglutination studies. The immune response of the inbred mice ranged from good to poor to none, depending on the H-2 type of the recipient strain. H-2 types a, k, s, and r responded well while H-2 types b, d, v, l, and q responded poorly or not at all. Since the immune response to IgA myeloma proteins was found to be associated with specific H-2 types, appropriate congenic strains were then similarly immunized to prove association of the Ir-IgA to the H-2 locus. Six congenic strains of mice from a2 and a4 immunoglobulin heavy-chain linkage groups, comprising four different H-2 types (a, k, d, and b), were immunized with BALB/c IgA myeloma protein. Corroboration of the preceding results was obtained. Finally, two recombinant strains of mice were immunized with the myeloma protein. Resultant chromosome mapping of the genes controlling the Ir-IgA showed that it is essentially in the same region as the Ir-1 of McDevitt and appeared to be on the right side of Ss, which itself is on the right side of the autosomal chromosome. However, a more precise localization is pending. It should be noted that most antibodies, especially in the congenic and recombinant strains of mice, were directed to Fab idiotypic specificities. This suggests that antibody response to  $C_H$  determinants is controlled by genetic systems other than or including H-2.

- 1814 SURFACE ANTIGENS OF MURINE LEUKEMIA CELLS AND MURINE LEUKEMIA VIRUSES. (E.) Aoki, T. (Sloan-Kettering Inst., New York, N.Y.). *Transplantation Proc* 3(3):1195-1198, 1971.

Murine leukemia viruses (MuLV) acquire an envelope during maturation by budding. As budding occurs along the plasma membrane, MuLV particles may acquire antigens which preexist at the site of viral maturation. A study was performed to determine possible acquired antigens preexisting at the site of maturation. Immunoelectronmicroscopy was used to study alloantigen systems  $\theta$ , Ly-A and Ly-B on mouse leukemia cells and the ascites leukemia K36. The antisera used were produced in congenic lines. Specimens for electron microscopic examination were labeled with southern bean mosaic virus or ferritin. Ly-B<sub>2</sub> was not found on the mouse leukemia cells, but H-2<sup>b</sup>,  $\theta$ -C3H and Ly-A.2 antigens were found on discrete areas of the cell surface. Thirteen percent of murine leukemia viruses produced by the mouse leukemia cells were  $\theta$ -C3H<sup>+</sup>, but H-2<sup>b</sup>, Ly-A.2 and Ly-B.2 antigens were not located on virus particles at any time. K36 cells are H-2<sup>k+</sup>,  $\theta$ -AKR<sup>-</sup>, Ly-A.2<sup>-</sup> and Ly-B.2<sup>-</sup>. These antigens are found in circumscribed areas on the cell surface. More than

25% of the viruses, budding or in free state, associated with K36 cells showed a limited H-2<sup>k+</sup> sector on the viral envelope. A discussion of the significance of these findings in relation to the site of emergence of MuLV from the cell surface is presented. The question of whether or not budding occurs in a random fashion is also discussed.

- 1815 AUTOIMMUNITY IN METHYLCHOLANTHRENE-INDUCED AND SPONTANEOUS THYROIDITIS IN BUFFALO STRAIN RATS. (E.) Silverman, D. A. (Ctr. Immunol., State U. New York, Buffalo) and N. R. Rose. *Proc Soc Exp Biol Med* 138(2):579-584, 1971.

Spontaneous, 3-methylcholanthrene (MC)-induced, and immunologically induced thyroiditis have been investigated in the Buffalo strain of inbred rat. Some Buffalo strain rats were fed a diet containing MC, others were actively immunized with crude rat thyroid extract in Freund's adjuvant and pertussis vaccine and others were held until spontaneous thyroiditis appeared. The level of circulating antibodies was measured at various intervals in all groups. Using hemagglutination assay and indirect immunofluorescence techniques it was found that circulating autoantibodies to thyroid antigen were present at high titers in each form of the disease. Tissue pathology in all cases was the same and double diffusion gel electrophoresis tests indicated that the antigen could migrate in the  $\alpha$ -globulin region. This evidence suggested that thyroglobulin was the immunologic stimulus, although other thyroid antigens might also play a role.

- 1816 IMMUNIZATION WITH CHEMICALLY MODIFIED LYMPHOMA CELLS. (E.) Prager, M. D. (U. Texas Southwestern Med. Sch., Dallas), I. Derr, A. Swann and J. Cotropia. *Cancer Res* 31(10):1488-1491, 1971.

An immunological study was conducted using C3H mice inoculated with 6C3HED ascites lymphosarcoma in an attempt to determine the efficiency of chemically modified tumor cells as a vaccine. Chemical modification of the cells was accomplished by reactions with: 1) diazotized *p*-aminobenzoic acid, 2) fluorodinitrobenzene, 3) iodoacetamide, 4) iodoacetate, 5) *N*-ethylmaleimide and 6) *p*-hydroxymercuribenzoate. The cells modified by 1 and 2 failed to protect against 10<sup>6</sup> 6C3HED cells; 3, 4 and 5 gave full protection; while 6 gave partial protection. The potent immunity was accomplished by blocking sulfhydryl groups with reagents generally not considered as good haptens. Iodoacetamide-treated EPF-1 lymphoma protected against an early transplant generation of EPF-1. The immune serum did not demonstrate cytotoxic antibody to 6C3HED or EPF-1; however, lymphoid cells obtained from an immune C3H mouse protected a susceptible animal, suggesting cell-mediated immunity.

- 1817 IMMUNOGENIC EFFICACY OF VARIOUS SYNGENEIC TUMOR CELL PREPARATIONS. (E.) Natale, N. (Sloan-Kettering Inst., New York, N.Y.), J. Reiner and C. M. Southam. *Cancer* 28(5):1118-1125, 1971.

The efficacy of different immunizing procedures in inducing immunity in C57BL/6 mice to challenge with cells of a methylcholanthrene-induced sarcoma was investigated. As a control to which mice immunized by other means could be compared, transplantation immunity to the methylcholanthrene-induced sarcoma was induced in some mice by implanting them with live tumor cells and then excising the resulting tumors. Mice rendered immune in this way were resistant to challenge with ten or 100 times the minimum number of methylcholanthrene-induced tumor cells which produced tumors in non-immunized mice (MTD); to 1000 times the MTD, however, mice rendered transplantation-immune were not resistant. To test the immunogenicity of irradiated tumor cells, tumor cells were exposed to 10,000 rads of  $\gamma$ -radiation from a  $^{60}\text{Co}$  source and administered in a single injection of one million cells. One million  $\gamma$ -irradiated cells were as or more effective in inducing immunity to tumor cell challenge than surgical excision of a growing tumor; immunization with 100,000 irradiated tumor cells, however, did not protect. After irradiation, cells could be stored at  $-70^\circ\text{C}$  with only partial loss of immunogenicity, but if stored at  $-20^\circ\text{C}$  cells were ineffective. Tumor cells given 100,000 rads of  $\gamma$ -irradiation were effective in inducing immunity to challenge but were less effective than cells exposed to 10,000 rads. The immunogenicity of living tumor cells contained in Millipore chambers which were implanted in mice i.p. or s.c. was also studied. Implantation of these chambers was protective, but afforded less protection against tumor cell challenge than excision of tumors or implantation of irradiated tumor cells. Although the chambers prevented the egress of tumor cells, they apparently did allow tumor-specific transplantation antigens to reach immunologically responsive host cells in an effective condition and in effective amounts.

- 1818 YEAST AND ANTITUMORAL ACTIVITY: A NEW CONTRIBUTION. (Fr.) Vermeil, C. (Fac. Med., Nantes, France), O. Morin and M. Marteau. *C R Acad Sci (Paris)* 273(12):1080-1082, 1971.

*Saccharomyces cerevisiae* modified by cycloheximide and by temporary introduction into a sarcomatous medium was found fully to protect mice vaccinated with  $4 \times 10^7$  blastophores/20 g body weight against a peritoneal graft of the ascitic sarcoma TG 180. The Charron strain of *Saccharomyces cerevisiae* (500 mg) was treated with 30 mg cycloheximide in 200 ml physiologic glucose solution (cycloheximide has no oncolytic effect on the TG 180 sarcoma) and inoculated into the peritoneum of a mouse with an ascitic sarcoma which had been growing for ten days. The harvested ascites which contained the yeast were subjected to a single freezing and thawing; the yeast cells were separated from sarcomatous cells by means of a series of filtrations through  $10 \mu$  mech metal filters. Preparations of washed cells were injected into mice and

a week following the fourth inoculation each mouse was injected i.p. with a suspension of live sarcomatous cells. Of 16 vaccinated mice 15 rejected the graft while the graft took in all of 25 control mice within three weeks. In a separate experiment residual sarcomatous cells present in the treated yeast cells were found to have no protective power; thus, the effect must be attributed to the treated yeast cells, specifically to glucan in the yeast cell walls. Untreated yeast imparted protection in 24% of cases. The role of cycloheximide in this phenomenon is as yet unclear; a linkage between tumoral antigens in the sarcomatous medium and the antitumoral determinants of glucan liberated from the mannan in the yeast cell wall is suggested as an explanation.

- 1819 THE IMMUNE REACTIVITY OF HETEROLOGOUS ANTISERA AGAINST A SOLUBILIZED HUMAN LYMPHOID MEMBRANE COMPONENT. (E.) Einstein, A. B., Jr. (Nat. Cancer Inst., Nat. Inst. Hlth., Bethesda, Md.), D. L. Mann, H. G. Gordon and J. L. Fahey. *Tissue Antigens* 1(5):209-218, 1971.

Using papain digestion and physicochemical fractionation, purified HL-A antigen bearing cell membrane components from human lymphoid cells was prepared. Antisera were produced in rabbits immunized with these components. The antisera showed high cytotoxic titers against lymphoid cells as well as other human tissue culture cells. Inhibition of the cytotoxicity was exhibited only by the membrane fractions that contained HL-A activity. The antisera were shown to possess antibodies against antigens shared by human and monkey, antigens common to different human tissues, lymphoid antigens and allotypic antigens by use of absorption and cytotoxicity inhibition studies. The purified human immunoglobulins were tested for their ability to inhibit the cytotoxic antisera to determine if the heterologous antisera reacted with immunoglobulin-like receptor sites on the lymphoid cell surface. Since these sera showed only minimal reactivity to nonlymphoid blood components, the heterologous antisera prepared against the human lymphoid cell membrane fraction could have been a more efficient immunosuppressive agent than an antisera prepared against whole cells or cell membranes.

- 1820 CELLULAR IMMUNITY AS A HOST RESPONSE TO SQUAMOUS CARCINOMA OF THE CERVIX. (E.) Goldstein, M. S. (Mount Sinai Hosp., New York, N.Y.), B. Shore and S. B. Gusberg. *Amer J Obstet Gynec* 111(6):751-755, 1971.

An immunological study of fourteen patients with proven invasive carcinoma of the cervix, one patient with adenocarcinoma and seven control patients is presented. The response of peripheral leukocytes to autologous tissue from invasive squamous cell carcinoma of the cervix was studied by the leukocyte-migration test. Fourteen patients showed leukocyte-migration inhibition when tested by autologous tumor. The seven control patients and the one patient



with adenocarcinoma did not show migration inhibition to cervical carcinoma antigen or to autologous normal cervix. Lymph nodes, containing squamous carcinoma cells, when used as the antigen in the migration test, demonstrated the inhibition phenomenon. Lymph nodes not invaded by tumor were negative in respect to the leukocyte-migration test. The results of the study indicated that a cellular immune mechanism is present in the host response to invasive squamous cell carcinoma of the cervix and suggested a possible correlation between round cell infiltrates, seen surrounding infiltrating squamous carcinomas of the cervix, with the cellular immune mechanisms.

1821 PARENTAL VARIANTS. (E.) Klein, E. (Karolinska Inst., Stockholm, Sweden). *Transplantation Proc* 3(3):1167-1171, 1971.

A study of cellular variation in terms of gene products was carried out. F<sub>1</sub> crosses were obtained between strain A mice and the three coisogenic lines ASW, ABY, and ACA. The resultant mice, differing genetically at the H-2 locus, were then subjected to methylcholanthrene injections to stimulate tumor growth. Once sarcomas were formed, transplantation was accomplished into the filial mice to determine homograft reaction. In mice which developed tumors, tumors were highly specific for genotype, the transplantation behavior being irreversible once selected; in addition, when transplant was carried out over successive generations, each variant subline was more specific as compared to the original tumor. Further information was obtained by immunogenicity (induction of antibody) tests and reactivity with specific antisera. It was found that the original tumor was asymmetric with regard to the expression of the two parental specificities, the cells apparently possessing a higher amount of one antigen than another. Additional genetic crosses and tumor transplantation techniques demonstrated that the loci controlling various types of antigen could be lost separately or together depending on their position relative to the centromere, and that some of these loci were not always necessary for cell viability since antigens could be regained over a period of time in the absence of loci. This regaining of antigens probably occurs because the cell surface of the tumor retains the antigens in reduced concentrations, these antigens being enhanced on stimulation. However, it is concluded that at least one set of H-2 antigens are needed for cellular viability of the tumor.

1822 CELL ANTIGENS OF YOSHIDA ASCITES HEPATOMA DETECTED BY MEANS OF CELLULAR ELECTROPHORESIS. (It.) Basso Ricci, L. (Pavia U., Italy) and L. Raimondi. *Boll Soc Ital Biol Sper* 47(8):236-240, 1971.

Electrokinetic potential variations were studied in Yoshida ascites hepatoma cells following contact with corresponding rabbit immune serum. Ascites cells from rat peritoneal fluid collected seven days after

inoculation with peritoneal fluid from rats with hepatomas were divided as follows: 1) nontreated cells; 2) cells washed with saline and subjected to contact with rabbit-immune serum for 30 min at 37°C; and 3) cells maintained in contact with immune rabbit serum as above but with no previous washing. Electrophoretic cell mobility was measured by liquid phase microelectrophoresis, which showed  $1.46 \times 10^{-4}$ ,  $0.866 \times 10^{-4}$  and  $0.686 \times 10^{-4}$  cm<sup>2</sup> V<sup>-1</sup>sec<sup>-1</sup>, respectively, for nontreated, washed and nonwashed ascites cells after contact with immune sera. Zeta potentials (V) of  $0.220 \times 10^{-4}$ ,  $0.1299 \times 10^{-4}$  and  $0.1029 \times 10^{-4}$  were computed for the three respective cell categories. Immune rabbit sera showed increased  $\gamma$ -globulin fractions upon electrophoresis when compared to normal serum. Immuno-electrophoresis of immune rabbit sera revealed increased  $\alpha$ -globulin and the appearance two fractions assumed to be IgA and IgG. Tumor ascites cells apparently can maintain their antigenic features for a considerable time following their transplantation.

1823 EXPRESSION OF MOLONEY LEUKEMIA VIRUS CONTROLLED CELL SURFACE ANTIGEN IN RELEASE TO VIRUS RELEASE. (E.) Fenyö, E. M. (Karolinska Inst., Stockholm, Sweden). *Transplantation Proc* 3(3):1185-1188, 1971.

The relationship between cell surface antigen and virus release was studied in cell hybrids produced by fusion of A9 mouse fibroblast cells, selected for resistance to 8-azaguanine and lacking the enzyme hypoxanthine-phosphoribosyltransferase, and two lines of Moloney virus-induced lymphomas (YAC and YACIR), differing in expression of the Moloney-type surface antigen and in the quantity of virus released. The hybrid cells expressed H-2<sup>k</sup> antigen (derived from both the A9 and lymphoma lines), the H-2<sup>d</sup> antigen (from the YAC and YACIR lines), the L cell antigen (from A9), and the Moloney-type surface antigen (fully expressed in YAC, partially expressed in A9, and suppressed in YACIR). All hybrid lines expressed the Moloney-type antigen to the same extent. However, differences were found in virus release. Whereas the YAC-A9 hybrids released infectious virus, the YACIR-A9 hybrids did not. From these results it was concluded that virus release and the expression of virus-induced membrane antigen are independent of each other. It was suggested that suppression of virus maturation in the YACIR-A9 hybrid may be due to a negative control imposed by the YACIR cell on its hybrid partner. These conclusions were also reached in a subsequent study on hybrids between A9 cells and various normal and neoplastic cells from mouse and human tissues. Of ten hybrid lines studied, two showed both the presence of viral membrane antigen and virus release, three lines lacked both properties, and the remaining five lines were discordant concerning the two properties. One of these lines releases infectious virus although the membrane antigen cannot be detected. Hybrids between A9 and an Ehrlich ascites tumor line and between A9 and a Burkitt lymphoma-derived line produced infectious virus. It was postulated that these two lines lack the factor which suppresses virus release.

- 1824 STIMULATING INFLUENCE OF BACILLUS CALMETTE-GUERIN ON IMMUNITY TO POLYOMA TUMORS AND SPONTANEOUS LEUKEMIA. (E.) Lemonde, P. (Inst. Microbiol., U. Montreal, Quebec, Canada), R. Dubreuil, A. Guindon and G. Lussier. *J Nat Cancer Inst* 47(5): 1013-1024, 1971.

Tubercle bacillus of the strain Calmette-Guérin (BCG) represses several types of experimental neoplasms, probably by stimulating immune responses to tumor-specific antigens; consequently the following experiments were performed. Inbred C3Hf mice were given no injections (controls) or were given various combinations of i.p. injections of polyoma virus and/or BCG. The mice were challenged with polyoma tumor cells from infected C3Hf mice four weeks after the initial immunization. The immunity induced by the polyoma virus to the syngeneic transplantation of polyoma tumors was increased in mice given the BCG before the virus; the incidence of tumor was reduced and the survival time of tumor-bearing mice was prolonged. Next, Syrian hamsters were pretreated like the C3Hf mice but challenge with polyoma cells was carried out three weeks after initial immunization. The results agreed with those of the previous experiment: the transplanted tumors were smaller, the growth rate was slower, and the instances of metastases were fewer in the hamsters given the BCG before the virus. Thirdly, AK mice of a line that spontaneously develops leukemia were either given no injections (controls) or combinations of injections of BCG and/or syngeneic leukemia cells. In AK mice given BCG before the leukemia cells the incidence of spontaneous leukemia was decreased and the appearance of leukemia and death from leukemia was delayed. The fourth experiment consisted of injecting C3Hf mice with polyoma cells plus lymphoid cells of mice previously immunized with polyoma virus and/or BCG. Lymph cells obtained after immunization of donor mice with virus alone were more effective in preventing tumors than those obtained after immunization of donor mice with both the virus and BCG. It can be inferred that the mechanism by which BCG affords protection against neoplasms may be a stimulation of active tumor immunity through an increase in lymphoid tissue; animals given BCG may be better equipped to cope with antigens of tumors and to resist neoplastic growth. However, such acquired immunity may not be effective in passive immunization.

- 1825 THE HL-A SYSTEM IN LYMPHOBLASTIC LEUKAEMIA: A STUDY OF PATIENTS AND THEIR FAMILIES. (E.) Lawler, S. D. (Royal Marsden Hosp., London, England), P. T. Klouda, R. M. Hardisty and M. M. Till. *Brit J Haemat* 595-605, 1971.

To determine the relationship of the HL-A system to neoplastic blood disease the HL-A phenotypes of 58 Caucasian children with acute lymphoblastic leukemia, as well as the phenotypes of parents and sibs, were studied. It was found that the reaction frequencies of the internationally defined HL-A antigens, HL-A 1, 2, 3, 10, and 11 at the first sublocus and HL-A 5, 7, 8, 12, and 13 at the second sublocus, did not differ in the patients or in their sibs or fathers from

normal controls. On the other hand, the mothers had a higher frequency of HL-A 11 antigen and a lower frequency of HL-A 13 antigen. FJH was the only antigen with a reaction frequency differing from the normal control value (3%) in patients (17%), fathers (13%), mothers (13%), and sibs (14%). The most important inference that could be drawn from this latter finding was that the FJH antigen, belonging to the second sublocus, was not preferentially coupled with any particular antigen at the first sublocus. It was also clear that the FJH antigen could be either paternally or maternally derived, that the segregation of the antigen was random, and that there was no deficiency of HL-A in the sibs. Finally, it was found that haplotypes occurring most frequently in the patients, parents, and sibs were also commonest in the control population. It is concluded that no particular HL-A phenotype or genotype is related to a predisposition to acute lymphoblastic leukemia; however, the high frequency of the FJH antigen needs to be investigated.

- 1826 IN VITRO STUDIES ON THE INHIBITORY EFFECT OF LYMPH-NODE CELLS: I. ANITUMOR ACTIVITY OF REGIONAL LYMPH-NODE CELLS FROM METHYLCHOLANTHRENE-INDUCED SARCOMA BEARING MICE ON THE SAME PRIMARY CULTURE SARCOMA CELLS. (E.) Ohsugi, M. (Okayama U. Med. Sch., Japan). *Acta Med Okayama* 24(1):447-456, 1970.

Ten C3H female mice bearing the H-2<sup>k</sup> locus were injected with the carcinogenic agent methylcholanthrene. As a result of these injections, several tumors were formed two of which were excised and harvested to provide viable tissues. This tissue was then cultured *in vitro* immediately after harvesting or was cultured after *in vivo* serial isograft transplantation. Lymphocytes were also obtained from both tumor-affected and normal mice. Lymphocytes were added to tumor cell suspensions; reactions to the mixing of lymphocytes and tumor cells were determined by tumor cell counts and by time lapse cinematography. It was found that small and intermediate size lymphocytes of tumor-affected mice aggregated on the surface of both cultured primary tumor cells and cultured cells of transplanted tumors, ultimately inhibiting the movement of the tumor cells and causing rupture of the tumor cell membrane. This antitumor activity increased steadily for the first few days, reached a peak after two weeks, and then diminished and disappeared. However, the antibody reaction was not found to be sufficient to inhibit tumor cell growth completely in any of the test cases, and the effect was dependent on the type of tumor cell present. Normal lymphocytes did not inhibit tumor cell growth, as they did not aggregate on either primary or isografted tumor cells.

- 1827 STUDY OF A SPECIFIC ANTIGEN OF HUMAN TUMORS OF THE COLON OF EMBRYONIC ORIGIN. (Fr.) von Kleist, S. (Sci. Res. Inst. Cancer, Villejuif, France). *Biol Med* 60(3):237-292, 1971.



The detection of a specific tumoral antigen of fetal origin, the isolation and characterization of the carcinoembryonic antigen (CEA), its localization in the cells of tissues from the rectal, sigmoid, ascending, transversal, and descending colon, and the presence of antibodies active against the CEA or against other components of tumors of the colon in serum of patients are described. Results are based on material from 565 tumors histologically identified as glandular epitheliomas and from 88 stomach tumors from adults and aborted fetuses. Extraction was performed in a saline neutral medium and in an acid medium. The antiserum was obtained from rabbits; the ring test, the Ouchterlony double diffusion reaction, immunoelectrophoresis and staining were used as analytical test methods. Three antigens were detected in colon tumors which were not found in the mucous membrane of the noncancerous colon. One of these, a normal antigen, is also present in the gastric mucosa. The second antigen is also found in a variety of other tumors; thus, only the third antigen of fetal origin of electrophoretic mobility beta seems to be specific for digestive tract tumors. Immunoelectrophoresis also disclosed that the antigen forms part of the plasma membrane of the cancerous cell although its role is unclear -- it may be a precursor. The appearance of the antigen in adults is related to malignant transformation rather than to the appearance of a tumor. Using physicochemical methods, the antigen was found to be a glycoprotein soluble in perchloric acid; it is of low molecular weight and has a tendency to polymerization. The study of antibodies circulating in the serum of patients suffering from cancer of the colon was inconclusive. The antibodies do not seem to be directed against CEA but against other as yet unidentified tissue constituents.

- 1828 SOME RECENT INFORMATION ON "BLOCKING ANTIBODIES" AS STUDIED IN VITRO. (E.) Hellström, I. (U. Washington Med. Sch., Seattle), K. E. Hellström, and H. O. Sjogren. *Transplantation Proc* 3(3):1221-1227, 1971.

New experimental results are presented and some published material is reviewed concerning the role of "blocking" serum factors which protect neoplasms from immunologic destruction in tumor-bearers, presumably by covering the tumor antigens. In certain experiments possible blocking effect of sera from several patients with a variety of malignant neoplasms was studied. It was found that the sera of 67 out of 81 patients blocked the cytotoxic effect of specifically immune lymphocytes. The effect was present when serum, lymphocytes and tumor cells were from the same patient or when lymphocytes and serum were from different donors with the same type of tumor as the patient from whom the target cells were taken. No blocking effect was seen when sera were tested against tumor cell types different from those of the serum donors. Blocking activity was seen in only three of 19 patients who were symptom-free after therapy; two of these subsequently suffered recurrences, with reappearance of blocking factor preceding recurrence. Loss of

blocking activity was also observed in one case of spontaneous remission. Evidence is presented indicating that the blocking antibodies of tumor-bearers may be an antigen-antibody complex. These hypothetical complexes were subjected to low acidity in an attempt to break them down, and then were subjected to ultrafiltration to separate the two components into a high molecular weight (> 100,000 or E 100) and a low molecular weight (between 10,000 and 100,000 or E 10) fraction. If such a complex exists, and could be separated, it was postulated that mixing the E 100 and E 10 fractions would reconstitute the complex and restore blocking activity. It was indeed found that, while the E 100 and E 10 fractions alone showed no blocking effect, activity was present in the reconstituted mixture. It was concluded that the most probable site of blocking factor action is on the immune lymphocytes since the E 10 alone showed a blocking effect if incubated with the test system for two days. It is also possible to demonstrate blocking antibody activity under certain conditions not involving neoplasia. These findings indicate apparent allograft tolerance, and in certain situations may involve the coexistence of immune lymphoid cells and also the coexistence of serum blocking factors which interfere with lymphocyte mediated cell destruction.

- 1829 IDENTIFICATION OF HUMAN T AND B LYMPHOCYTES IN NORMAL PERIPHERAL BLOOD AND IN CHRONIC LYMPHOCYTIC LEUKAEMIA. (E.) Wilson, J. D., (Hall. Inst. Med. Res., Victoria, Australia) and G. J. V. Nossal. *Lancet* 2(7728):788-791, 1971.

Peripheral blood lymphocytes were studied from 11 normal individuals, three patients with chronic lymphocytic leukemia (CLL), and one with lymphoblastic leukemia. Two populations of lymphocytes were detected by a sandwich radioimmunolabeling technique. A mean of 34% of cells from peripheral blood exposed for 30 min to an  $I^{131}$ -labeled gamma globulin fraction were labeled in specimens from healthy people. A second population of lymphocytes showed a relatively insignificant amount of labeling. Thymocytes showed only one population of cells with very little detectable immunoglobulin on their cell surface. The only difference in the two lymphocyte populations was in size, with labeled cells being larger than the unlabeled population. More than 85% of the lymphocytes of the CLL patients were labeled and these possessed more immunoglobulin than lymphocytes or the majority of normal blood lymphocytes. Labelling patterns suggested that lymphocytes from CLL patients constituted a single population, although differences existed between the three patients studied. Almost no surface immunoglobulin could be detected on cells from the patient with acute lymphoblastic leukemia. It is proposed, by analogy with observations in mice, that the two groups of lymphocytes represent bursa-dependent (cells with high surface immunoglobulin density) and thymus-dependent (low immunoglobulin density) lymphocytes.

- 1830 BINDING OF CONCAVALIN A TO NORMAL AND TRANSFORMED CELLS AS DETECTED BY IMMUNO-FLUORESCENCE. (E.) Mallucci, L. (Royal Postgrad. Med. Sch., London, England). *Nature New Biol* 233:241-244, 1971.

Binding of concanavalin A (Con A) detectable by immunofluorescence was found to occur in both normal and transformed mouse cells. Polyoma virus-transformed cells untreated with trypsin were observed to agglutinate in the presence of Con A. The response was related to dose. Normal cells and cells transformed by methylcholanthrene did not agglutinate under these conditions. Immunofluorescence techniques, however, revealed that both normal and transformed cells were able to bind Con A. The degree of staining was not related to cell density. Polyoma-transformed cells showed staining in large, localized areas of the membrane. The intensity of staining was less in all other cell lines. Both normal and transformed cells treated with 0.2% trypsin at 37°C lost the ability to bind Con A; however, binding gradually returned to normal values in about eight to ten hours, the same time previously shown to be required for regeneration of the cell coat. Data also indicate a relationship between coat thickness and the degree of binding of Con A. Since Con A could be bound by both normal and transformed cells, it was concluded that, at least in this system, binding sites on normal cells are not in a cryptic form. Since agglutination occurred only with the polyoma-transformed cells and not with the methylcholanthrene-transformed or normal cells, it was also concluded that agglutination is not necessarily related to the oncogenic state. The ability of normal cells to agglutinate after digestion with trypsin can be explained by changes in the coat structure and by reorganization of binding sites.

- 1831 DEVELOPMENT OF ERYTHROCYTE MEMBRANE-SPECIFIC ANTIGEN(S) IN CLONAL CULTURED CELLS OF FRIEND VIRUS-INDUCED TUMOR. (E.) Furusawa, M. (Fac. Sci., Osaka City U., Japan), Y. Ikawa and H. Sugano. *Proc Jap Acad* 47(2):220-224, 1971.

It has been shown that Friend virus-induced tumor cells can either revert or differentiate to erythrocyte-like corpuscles; however, it was not known whether the erythrocyte-like cells synthesized membrane-specific antigens. Two clonal cell lines (1 and 2) were derived from mouse splenic lesions induced by Friend virus to test for this possibility; normal cells were tested as controls. Samples of these cells were maintained either *in vitro* or placed in diffusion chambers, the whole being inserted into the peritoneal cavity of male DDD mice. Cells were examined microscopically and also biochemically by fluorescein-labeled antiserum and agglutination testing. It was found that clone 1 cells *in vitro* proved to be cytologically erythroblastic, while labeled-antibody staining and the mixed agglutination test gave negative results, showing that tumor cells lacked antigens specific to the erythrocyte membrane of the

mouse. However, the same cells *in vivo* showed marked reactions with erythrocyte membrane-specific antibody, although they were smaller in size than normal erythrocytes. It is inferred that the fluorescein-positive erythrocyte-like cells were newly formed, possibly by extrusion of the nuclei from the tumor cells during the chamber culture. It was also discovered that cell cultures *in vivo* gave a typical mixed-agglutination reaction, indicating synthesis of erythrocyte-specific surface antigens by tumor cells while they were cultured in the chamber. The Friend virus-induced tumor cells can fully retain erythropoietic potency *in vitro* for a very long period of time; further, a change analogous to reversion or differentiation of the tumor cells along erythropoietic lines is possible.

- 1832 CELL CYCLE-DEPENDENT IMMUNE LYSIS OF MOLONEY VIRUS-TRANSFORMED LYMPHOCYTES: PRESENCE OF VIRAL ANTIGEN, ACCESSIBILITY TO ANTIBODY, AND COMPLEMENT ACTIVATION. (E.) Lerner, R. A. (Scripps Clin. Res. Fdn., La Jolla, Calif.), M. B. A. Oldstone and N. R. Cooper. *Proc Nat Acad Sci USA* 68(10):2584-2588, 1971.

The presence of surface viral antigen, the availability of this antigen to antibody, and the nature and extent of activation of the complement system by antiviral antibody in the course of the cell cycle of Moloney virus-transformed lymphocytes were examined. Mouse lymphoma YCAB cells were analyzed by indirect immunofluorescence to determine the presence of surface viral antigen. It was found that the surface antigen was present but distributed nonuniformly; instead, the surface viral antigen was spread in a crescent over only a portion of the cell, with the crescent remaining unchanged throughout the various growth stages of the cultured cell population. The activation of complement after antibody-virus union was then determined using purified human complement components, and the ability of synchronized YCAB cells plus anti-viral antibody to activate the complement system was appraised. The cell population in the logarithmic growth phase was able to activate the complement system. Although the consumption of complement by the YCAB cells was observed in the absence of specific antibody at all phases of the cell cycle, there was a significant increase in complement utilization on addition of specific antiviral antibody. Cytotoxicity was found to be confined to the stationary phase of growth ( $G_1$ ). Cell resistance to the cytotoxic effects of antibody and complement at phases of the cell cycle other than  $G_1$  can be explained by the following: 1) the complement reaction may not occur on the cell surface but rather may proceed in free solution at a distance from the target cell surface; 2) there may be cell cycle related changes in configuration, charge, or structure of the plasma membrane that render it resistant to cytotoxicity; or 3) the ability of the cell to repair damage to the plasma membrane may differ during the cycle. However, it is impossible to differentiate among these possibilities on the basis of present data.



- 1833 ANTI-EB VIRUS ANTIBODY TITER IN SERA COLLECTED FROM HUMAN SUBJECTS OF SURABAJA, INDONESIA, IN 1968. (E.) Ito, Y. (Aichi Cancer Ctr. Nagoya, Japan), A. Ishimoto, T. Hosokawa, S. Hotta, and B. Noerjasin. *Kobe J Med Sci* 16:261-265, 1970.

This study was carried out primarily to survey the general pattern of distribution of anti-Epstein-Barr virus (EBV) antibody titer among the people of Surabaya, Indonesia, and to search for another disease which might evoke the rise of anti-EBV titer. To accomplish both of these objectives, serum was drawn from healthy adults and children and also from patients suffering from hemorrhagic fever; serum was then subjected to indirect immunofluorescence studies. It was found that the distribution pattern of the anti-EBV antibody titer among various age groups showed little variation from that usually found with the anti-EBV antibody titer among Japanese normal subjects. In addition, it was discovered that hemorrhagic fever caused no unusual rise of the anti-EBV antibody titer.

- 1834 SUSCEPTIBILITY TO LEUKEMIA: IMMUNOLOGIC FACTORS IN DOWN'S SYNDROME. (E.) Sutnick, A. I. (Inst. Cancer Res., Philadelphia, Pa.), W. T. London, B. S. Blumberg and B. J. S. Gerstley. *J Nat Cancer Inst* 47(5):923-933, 1971.

A study was conducted on a Down's syndrome (DS) population and on other mentally retarded controls to determine the immunologic and hematologic factors associated with the increased susceptibility to leukemia found in DS patients. The presence of Australia antigen (Au[1]) a particle found in the blood of persons with acute hepatitis, was investigated by the micro-Ouchterlony method. Tuberculin (purified protein derivative [PPD]), histoplasmin, mumps, monilia, trichophyton, and streptokinase skin tests were then performed. Differential WBC counts and fasting blood sugar analyses were performed, both alone and in response to epinephrine injections. Patients with DS had a significantly lower total index of skin reactivity, principally related to a decreased response to mumps antigen and PPD. There was also a lower total lymphocyte count and a higher basophil count in all DS patients, plus a general rise in the white blood cell count after epinephrine injections and a higher fasting blood sugar. Lastly, Au(1) was found in one third of the patients with DS. A possible interpretation of these studies is that patients with DS have a defect in their small lymphocyte function. It was known that the  $\gamma$ G immunoglobulins of institutionalized DS patients are significantly elevated. Possibly the small lymphocyte defect of DS patients is compensated for by an elevated response of the humoral immune mechanism. If immunologic defects such as this can be demonstrated in other leukemia-prone groups, then abnormalities may presage the onset of malignant blood disease.

- 835 IMPAIRED LYMPHOCYTE REACTIVITY AGAINST TUMOUR CELLS IN PATIENTS WITH COELIAC DISEASE.

(E.) Maclaurin, B. P. (Dept. Exp. Path., U. Birmingham, England), W. T. Cooke and N. R. Ling. *Gut* 12(10):794-800, 1971.

A study in which lymphocytes from patients with coeliac disease showed impaired reactivity against cultured lymphoma cells is presented. Cytotoxic capacity of unstimulated lymphocytes and of lymphocytes prestimulated with irradiated Burkitt's lymphoma cells (EB cells) was assessed by the addition of  $^{51}\text{Cr}$ -labeled EB cells to cultures of lymphocytes. A significant drop in the proliferative and cytotoxic capacity of lymphocytes of patients with coeliac disease was seen as compared to normal lymphocytes. An inhibiting factor in sera of coeliac disease patients, as well as an intrinsic defect in cellular immune response, apparently account for the impaired responsiveness. This impaired response *in vitro* may indicate a comparable defect in the *in vivo* immune surveillance system. This would explain the known increase of lymphosarcoma in patients with longstanding coeliac disease as well as the increased incidence of other gut-related tumors in such patients.

- 1836 KINETICS OF SYNTHESIS AND RATE OF DEGRADATION OF T ANTIGEN INDUCED BY POLYOMA VIRUS. (E.) Nicoli, J. (Admiralty Hlth. Service, Marseilles, France), G. Meyer and M.-R. Martin. *J Gen Virol* 13(2):331-334, 1971.

The small-plaque Toronto strain of polyoma virus was inoculated onto cultures of mouse embryo fibroblasts to study the kinetics and renewal rate of T antigen. After infection the cultures were exposed to tritiated leucine followed by isolation of nuclei. The nuclear pellets were used as the sources of solubilized labeled nuclear proteins from which the T antigen was identified and titrated by radioimmunologic methods; anti-T serum was added to the radioactive proteins and incubated with antiglobulin hamster serum. Precipitates formed by this technique were filtered and the filtrate was subjected to liquid scintillation counting. It was found that synthesis of the T antigen began before the tenth hour after infection, reached its maximum at the eighteenth hour, and decreased rapidly after the twentieth hour, thus confirming the earlier classical immunofluorescence data. In addition, the degradation rate indicated that there was little variation between the sixteenth and twenty-first hours. It is concluded that T antigen is a protein of high turnover rate, which seems to imply that T antigen plays an important role in the infectious cycle. The possibility that the T antigen may be a precursor of an early functional protein is currently under investigation by the authors.

- 1837 SPECIFIC BINDING OF ANTIGEN OF LYMPHOCYTES: EVIDENCE FOR LACK OF UNISPECIFICITY IN ANTIGEN-BINDING CELLS. (E.) Miller, A. (Dept. Bacteriol., U. California, Los Angeles, ), D. DeLuca, J. Decker, R. Ezzell and E. E. Sercarz. *Amer J Path* 65(2):451-465, 1971.

Bone marrow, spleen, thymus, and lymph node cells, derived from mouse tissue, were pretreated and then subjected to various biochemical tests to determine whether unispecificity exists in lymphocytes. Lymphoid cells were exposed to fluorescein conjugated  $\beta$ -galactosidase. It was found that from 30,000 to almost one million molecules were present on single cells. This large range in the number of molecules suggests a broad heterogeneity in receptor sites. Further tests were carried out using 5-bromo-4-chloro-3-indolyl- $\beta$ -D-galactoside (BIG), in order to localize receptors. Most of the positive cells were medium or small lymphocytes, presenting a variety of localization patterns of patchy appearance. Through use of 3-amino-9-ethyl carbazole (CAR) and hydrogen peroxide it was determined that horseradish peroxidase also had receptor sites on small and medium lymphocytes. By combining the BIG and CAR tests, it was deduced that some cells could be double binders of both galactosidase and peroxidase, with separate regions for binding each enzyme. Saturation curves, acridine orange staining, removal of macrophages and other tests were used to test for artifacts, but results indicated that there was no reason to doubt any of the responses obtained. Many supportive studies were reviewed and the conclusion was drawn that multiple-binding cells do exist. A model was proposed to explain this conclusion.

- 1838 SPECIFICITY OF ANTIBODIES AGAINST HUMAN IgG MYELOMA PROTEINS PRECIPITATING NEITHER FAB NOR Fc FRAGMENTS. (E.) Medgyesi, G. A. (Natl. Inst. Haematol. Blood Transfusion, Budapest, Hungary), M. Pakh and J. Gergely. *Haematologia* 5(1-2):99-107, 1971.

The behavior of antisera directed against human IgG myeloma proteins is described. The reactivity of the sera was examined with various IgG myeloma proteins to determine if the individual or the subclass specificity of the proteins may be recognized by the sera. Normal and myeloma IgG proteins were isolated and subjected to a preparation of guinea pig antisera, with immunoelectrophoresis and radial double diffusion assays being performed. Of the ten antisera produced against four different myeloma proteins, all but one precipitated either or both of the Fab or Fc fragments. The antiserum not precipitating any of the fragments produced strong precipitation lines only with the homoantigen, possibly indicating that individual antigenic specificity of myeloma proteins depends upon the steric conformation of the protein molecule. A study of the relationship of the antigen to the polypeptide chains was carried out. It was discovered that the antigens were related to the heavy rather than the light chain of the homoantigen; the presence of both chains of the initial protein were needed for full expression of the antigens.

- 1839 DELETION OF EPITHELIAL ABH ISOANTIGENS IN PRIMARY GASTRIC NEOPLASMS AND IN METASTATIC CANCER. (E.) Sheahan, D. G. (Boston City Hosp., Mass.), S. A. Horowitz and N. Zamcheck. *Amer J Dig Dis* 16(11):961-969, 1971.

A study using the mixed cell agglutination reaction to determine the presence or absence of A, B and H isoantigens in primary gastric neoplasms and in metastatic cancer is reported. In eight out of nine gastric epithelial malignancies, the A, B and H isoantigens were reduced or absent. There was a complete absence of isoantigenic activity in all metastases but some residual activity was noted in three of the corresponding primary gastric tumors. Eight of the nine gastric tumor patients showed intestinalization of the gastric mucosa. Intestinalized metaplastic epithelium showed a loss of isoantigenicity similar to that seen in tumors. The partial retention of such isoantigenicity in tumor tissue was shown in two patients with pernicious anemia. The results of this study suggested that an alteration of blood-group substance syntheses occurred in malignant epithelium, however, it was not known if they caused or were a result of malignant change. It was possible that loss of antigenicity may have aided the ability of malignant cells to metastasize.

- 1840 ROUS VIRUS-INDUCED RESISTANCE AGAINST MOUSE ROUS TUMOR CELLS. (Rus.) Kryukova, I. N. (Gamaleya Inst. Epid. Med. Moscow, U.S.S.R.), O. V. Babkova and I. B. Obukh. *Vop Onkol* 17(8):81-85, 1971.

The possibility of inducing resistance in adult mice to isologous Rous tumor cells by means of preliminary immunization with highly oncogenic Rous virus variants, such as Carr-Zilber (C-Z), ShC3H, Schmidt-Ruppin and Dyadkovska, was made. Immunization was accomplished with intra-abdominal Rous virus preparation (30% chicken tumor homogenate), in doses of 0.007-0.6 ml, depending on age. Different numbers of threshold doses of test tumor cells were introduced subcutaneously eight, 14-17 and 35-37 days after immunization. The average latency period of Rous virus-induced tumors was found to be six to seven weeks. Low but statistically reliable resistance to a small number of tumor cell threshold doses was found for one (C-Z) of the four variants only. Immunization with virus variants produced greater resistance in sucklings than in adult mice. The resistance phenomenon could not be reproduced by means of Rous viruses in adult mice. No tumor-specific transplantation antigen was revealed during the first two weeks preceding tumor formation.

- 1841 THE G<sub>IX</sub> SYSTEM: A CELL SURFACE ALLO-ANTIGEN ASSOCIATED WITH MURINE LEUKEMIA VIRUS; IMPLICATIONS REGARDING CHROMOSOMAL INTEGRATION OF THE VIRAL GENOME. (E.) Stockert, E. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.), L. J. Old and E. A. Boyse. *J Exp Med* 133(6):1334-1355, 1971.

A new cell surface antigen (G<sub>IX</sub>; G=Gross) which exhibits mendelian inheritance and appears *de novo* in cells that become productively infected with MuLV (Gross), the wild-type leukemia virus of the mouse, is investigated. In normal mice, G<sub>IX</sub> is a cell surface allo-antigen confined to lymphoid cells and found in highest amount on thymocytes. Four categories of in-



- bred mouse strains can be distinguished according to how much G<sub>IX</sub> antigen is expressed on their thymocytes. G<sub>IX</sub><sup>-</sup> strains have none; in the three G<sub>IX</sub><sup>+</sup> categories, G<sub>IX</sub><sup>3</sup>, G<sub>IX</sub><sup>2</sup>, and G<sub>IX</sub><sup>1</sup>, the amounts of G<sub>IX</sub> antigen present (per thymocyte) are approximately in the ratios 3:2:1. A study of segregating populations derived mainly from strain 129 (the prototype G<sub>IX</sub><sup>3</sup> strain) and C57BL/6 (the prototype G<sub>IX</sub><sup>-</sup> strain) revealed that two unlinked chromosomal genes are required for expression of G<sub>IX</sub> on normal lymphoid cells. The phenotype G<sub>IX</sub><sup>+</sup> is expressed only when both genes are present, as in 129 mice. C57BL/6 carries neither of them. At one locus, expression of G<sub>IX</sub> is fully dominant over nonexpression (G<sub>IX</sub> fully expressed in heterozygotes). At the second locus, which is linked with H-2 (at a distance of 36.4±2.7 units) in group IX (locus symbol G<sub>IX</sub>), expression is semidominant (50% expression of G<sub>IX</sub> in heterozygotes); gene order T:H-2:Tla:G<sub>IX</sub>. As a rule, when cells of G<sub>IX</sub><sup>-</sup> mice or rats become overtly infected with MuLV (Gross), their phenotype is converted to G<sub>IX</sub><sup>+</sup>. So far the only example of G<sub>IX</sub><sup>-</sup> → G<sub>IX</sub><sup>+</sup> conversion taking place without overt MuLV infection is represented by the occurrence of GCSA<sup>+</sup>:G<sub>IX</sub><sup>+</sup> myelomas in BALB/c (GCSA<sup>+</sup>:G<sub>IX</sub><sup>-</sup>) mice. G<sub>IX</sub> antigen sometimes occurs independently of productive MuLV infection; for example, thymocytes and some leukemias of 129 mice are GCSA<sup>+</sup>:G<sub>IX</sub><sup>+</sup>, and MuLV-producing sarcomas may be GCSA<sup>+</sup>:G<sub>IX</sub><sup>-</sup>. The frequent emergence of cells of G<sub>IX</sub><sup>+</sup> phenotype in all mouse strains implies that the structural gene coding for G<sub>IX</sub> antigen is common to all mice.
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- 1843 HL-A SPECIFICITIES IN ACUTE AND CHRONIC LYMPHATIC LEUKEMIA. (E.) Walford, R. L. (UCLA Sch. Med., Los Angeles, Calif.), E. Zeller, L. Combs and P. Konrad. *Transplantation Proc* 3(3): 1297-1300, 1971.
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- 1845 ANTIGENIC EXPRESSION AS AN ESCAPE ROUTE FROM IMMUNOLOGICAL REJECTION: POSSIBLE EXAMPLES OF ANTIGENIC MODULATION AFFECTING H-2 ANTIGENS AND CELL-SURFACE IMMUNOGLOBULINS. (E.) Takahashi, T. (Sloan-Kettering Inst., New York, N.Y.). *Transplantation Proc* 3(3):1217-1220, 1971.
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- 1854 IMMUNOSUPPRESSION: A MEANS TO ASSESS THE ROLE OF THE IMMUNE RESPONSE IN ACUTE VIRUS INFECTIONS. (E.) Nathanson, N. (Sch. Hyg. Publ. Hlth., Johns Hopkins U., Baltimore, Md.) and G. A. Cole. *Fed Proc* 30(6):1822-1830, 1971.
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- 1879 BLASTIC TRANSFORMATION OF HUMAN LYMPHOCYTES: INHIBITORY EFFECTS BY ANTI-HL-A SERA. (It.) Popisil, M. (Czechoslovak Acad Sci, Prague), T. Meo, A. O. Carbonara and R. Ceppellini. *G Batt Virol Immun*, 63(11-12):860-874, 1970.

## See also:

- \* (Rev): 1509, 1510, 1512, 1516, 1522
- \* (Chem): 1573, 1610
- \* (Phys): 1659
- \* (Viral): 1697, 1700, 1719, 1764, 1771
- \* (Path): 1893

- 1880 PROLIFERATIVE CELLS IN THE HUMAN SEBA-CEOUS GLAND: LABELLING INDEX REGIONAL VARIATIONS. (E.) Plewig, G. (Dept. Dermatol., U. Munich, Germany), E. Christophers and O. Braun-Falco. *Acta Dermatovener* 51(6):413-422, 1971.

Proliferative activity of sebaceous glands obtained from specimens of the back, scalp and forehead of 63 healthy men was studied by means of planimetry and tritiated thymidine autoradiography. Each sebaceous gland was divided into two cell populations, a differentiating cell pool (DCP) and an undifferentiated cell pool (UCP), according to morphology and labelled precursor uptake. Label was found in the basal layer of the acini 45 min postinjection. Labelling index (L.I.) was found to have the highest values on the forehead (10.0%). Both back and scalp showed a lower L.I. (8.9% and 8.6%, respectively). These differences were statistically significant. All three regions showed the same general L.I. pattern within the two classes of cells, with the UCP having a value about twice that of the DCP ( $P < 0.001$ ). Planimetry showed that sebaceous glands of the back were two to three times larger than those of the scalp or forehead. A good correlation was found between the number of labelled cells and the cross-sectional area of the gland. It was concluded that the UCP may be a population of rapidly proliferating basal cells which serve as precursors to the sebaceous gland.

- 1881 ASSOCIATION OF ATYPICAL CHARACTERISTICS OF BENIGN BREAST LESIONS WITH SUBSEQUENT RISK OF BREAST CANCER. (E.) Black, M. M. (New York Med. Coll., N. Y.), T. H. C. Barclay, S. J. Cutler, B. F. Hankey and A. J. Asire. *Cancer* 29(2):338-343, 1972.

A retrospective case-control study was carried out to determine to what degree atypical changes in the mammary duct system are associated with increased risk of developing breast cancer. A previously developed grading system was used to describe the morphological atypicality in a series of benign breast lesions. The primary finding is that a woman with some degree of ductular atypia in a benign lesion is subject to a risk of developing breast cancer five times greater than that of a woman with no evidence of atypical changes. The implications of this finding regarding treatment require further study.

- 1882 TRANSFORMATION OF *AGROBACTERIUM TUMEFACIENS* INTO A NON-ONCOGENIC SPECIES BY AN *ESCHERICHIA COLI* RNA. (E.) Beljanski, M. (Inst. Pasteur, France), M. Beljanski, P. Manigault and P. Bourgairel. *Proc Nat Acad Sci* 69(1):191-195, 1972.

Transforming RNA excreted by mutants of *E. coli* ML 30 Shor resistant to showdomycin was purified and used to treat wild type *Agrobacterium tumefaciens*, strain B<sub>6</sub>, a plant oncogenic bacterium. Complete and partial transformants were isolated and characterized. Complete transformants were nononcogenic and grew more rapidly than untransformed bacteria. Unlike the par-

tial transformants, the complete ones lost all reactivity with anti-B serum; cell metabolism was also altered in complete transformants. Sucrose gradient analysis showed that ribosome components were altered in transformants. Electrophoresis of transformed cell RNA indicated an increase in the 23S component and decreases in the 16S and 17S moieties. Purine content was increased in transformant RNA, and ribosomal proteins were also altered. It is suggested that the complete transformant may represent a "new species."

- 1883 ARGENTAFFIN CELLS IN PROSTATIC CARCINOMA: DIFFERENTIATION FROM LIPOFUSCIN AND MELANIN IN PROSTATIC EPITHELIUM. (E.) Azzopardi, J. G. (Royal Postgrad. Med. Sch. London, England) and D. J. Evans. *J Path* 104(4):247-251, 1971.

It has been found that argentaffin cells, morphologically similar to enterochromaffin cells of the gastrointestinal tract, are associated with normal and hyperplastic human prostates in 80% of the cases studied. These cells have the same histologic appearance in both normal and malignant tissue. Quantitatively, the argentaffin cells are extremely few, but these cells may be more numerous in some cases. Qualitatively, they may be differentiated from acinar epithelial cells which frequently contain prolipofuscin or lipofuscin. It is thought that these cells arise by divergent differentiation during early malignancy of some prostatic neoplasms, and that their presence may have a bearing on metabolic effects, particularly on polypeptide secretion.

- 1884 GENE ACTIVATION IN WI-38 FIBROBLASTS STIMULATED TO PROLIFERATE: REQUIREMENT FOR PROTEIN SYNTHESIS. (E.) Rovera, G. (Temple U. Sch. Med., Philadelphia, Pa.), J. Farber and R. Baserga. *Proc Nat Acad Sci USA* 68(8):1725-1729, 1971.

WI-38 human diploid fibroblasts were grown to confluency and stimulated to proliferate by replacing the old medium with new. Up to 80% of the contact inhibited cells could be stimulated to synthesize DNA. Cycloheximide was added to the cultures at various intervals to inhibit protein synthesis to study the relationship between protein synthesis and increased template activity of chromatin isolated from stimulated cells. It was discovered that WI-38 cell viability was not impaired by exposure to cycloheximide, and that induction of DNA synthesis was dependent on proteins synthesized in the first hour after application of the stimulus. Cycloheximide inhibited increase in template activity of chromatin isolated from stimulated cells; specifically, cycloheximide inhibited acidic nuclear proteins. Thus, protein synthesis was required for chromatin template activity. It was also shown that when cycloheximide inhibits certain protein synthesis, it may at the same time derepress other genes which act when cellular proliferation is not taking place. Actinomycin D, which inhibits RNA synthesis, was not found to affect template activity. These



results lead to two conclusions: 1) RNA molecules newly synthesized on a DNA template do not regulate the early increase in template activity of cells stimulated to proliferate; and 2) DNA-dependent RNA synthesis is not necessary for synthesis of those proteins required for the increase in template activity, suggesting that stimulating factors for DNA synthesis act on cells at a post-transcriptional level, triggering synthesis of gene regulator proteins from previously formed messages.

- 1885 CONGENITAL NEPHROMA OF INFANCY: INDUCTION OF RENAL STRUCTURES BY ORGAN CULTURE. (E.) Crocker, J. F. S. (U. Minnesota Hosp. Minneapolis) and R. L. Vernier. *J Pediatr* 80(1):69-73, 1972.

A benign renal tumor, characterized by interlacing fascicles of spindle cells with round-to-oval hyperchromic nuclei, was removed from a two-day-old infant. The tumor tissue was sectioned, and small blocks were placed in organ culture contiguous to pieces of fetal mouse brain or spinal cord. After 48 hr, the tumor tissue showed clumping of the cells into spherical sections, and at 96 hr, typical S-shaped fetal nephrons, including recognizable Bowman's capsules, glomeruli, and proximal tubules, were apparent. It was concluded that this type of renal tumor, resembling Wilm's tumor, was of nephrogenic origin. Failure of the tissue to develop normally in an *in vivo* situation could be the result of a qualitative or quantitative inadequacy in "inducer substance", which is known to cause cellular differentiation.

- 1886 THE ULTRASTRUCTURE OF PREINVASIVE CANCER OF THE CORNEAL EPITHELIUM. (E.) Tripathi, R. C. (Inst. Ophthalmol., U. London, England) and A. Garner. *Cancer Res* 32(1):90-97, 1972.

A corneal epithelial lesion suspected of being malignant was removed from an 80 year old male. Half of the specimen was fixed and prepared for study under the light microscope and the other half was prepared for electron microscopy. Light microscopic study revealed hypercellularity with individual cells showing an increased nucleocytoplasmic ratio with distinct loss of polarity. Cell nuclei were hyperchromatic, enlarged, and frequently had two or more prominent nucleoli. Mitotic figures were plentiful and multilobulated nuclei and multinucleated cells were not uncommon. Intercellular spaces were abnormally wide in some areas with well-defined intercellular bridges. Other areas had less obvious intercellular spaces showing increased staining of many of the basal and mid-epithelial cells. The basement membrane was intact and no abnormality was seen in the underlying Bowman's membrane. Essentially the same picture was seen under the electron microscope. There was loss of normal architecture in the basal layers with variation in cell size and shape. The number of hemidesmosomal attachments to the basement membrane was reduced in some areas. Intercellular cytoplasmic borders were often straight or smooth due to close packing of cells and reduction in the

number and extent of interdigitating processes. Although desmosomes were reduced in number, their pattern was normal. Some areas, however, showed a disturbance of desmosomal-tonofilament attachments associated with widened intercellular spaces. The middle layers of the epithelium showed a similar loss of polarity with cell pleomorphism. Changes in the superficial layers paralleled those of the deeper layers except that loss of polarity was less obvious. Nuclear and cytoplasmic abnormalities were also observed. Nuclear chromatin tended to be granular, ribonucleoprotein granules were prominent, and nucleoli were often multiple and enlarged. Cytoplasmic changes included fasciculation of tonofilaments into dense bundles often showing a conspicuous perinuclear arrangement. Cytoplasmic organelles were increased in number and were largely concentrated around the nucleus. Perinuclear tonofilament bundles of dividing cells tended to be randomly oriented. Loss of intercellular contact was associated with incorporation of desmosome-like structure within the cytoplasm.

- 1887 THE CELLULAR MANIFESTATIONS OF MICROINVASIVE SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX. (E.) Ng, A. B. P. (U. Hosp., Cleveland, O.), J. W. Reagan and E. A. Lindner. *Acta Cytol* 16(1):5-13, 1972.

Specimens were obtained by cervical scraping and aspiration of the cervical canal from 52 women with microinvasive cancer seen at the Institute of Pathology of the University Hospitals of Cleveland and Case Western Reserve University between 1943 and 1967. The cellular characteristics of microinvasive cancer are described and histologic changes are compared to those seen in dysplasia, carcinoma *in situ* and invasive cancer. The abnormal cells seen on the smears were small, having a mean area approximately one-fifth that of normal squamous cells. Mean nuclear area of microinvasive cells ( $88.2 \pm 39.2 \mu^2$ ) was more than twice that of normal cells. An adverse host response consisting of exudate and/or transudate, fresh and lysed erythrocytes, fibrin and cell debris was seen in 32 of the 52 cases. The degree of response was apparently related to the presence of surface ulceration and was generally less marked in microinvasive cancer than in frank carcinoma. Cells characteristic for microinvasion were usually arranged in syncytia, seldom occurring singly, as was the characteristic pattern of invasive carcinoma. Coarse clumping of chromatin with marked nuclear clearing, a characteristic of frank squamous cell cancer, was not conspicuous although chromatin was irregularly distributed in microinvasive cells. Approximately two-thirds of the cases of microinvasion showed cellular and nuclear pleomorphism, disorganized cellular polarity, focal cellular differentiation and the presence of nucleoli, features not commonly associated with dysplasia or carcinoma *in situ*. The number of abnormal cells in cell samples increased with increasing penetration. Microinvasive cancers having penetrations of 0.1 to 2.0 mm resembled carcinoma *in situ* whereas microinvasion of from 3.1 to 5.0 mm most closely resembled outspoken cancer. A tumor diathesis was

present in one-third of the cases of early microinvasion and absent in carcinoma *in situ*. Pyknotic cells were infrequent in microinvasive cancer but were relatively common in frank cancer and unusual in dysplasia and carcinoma *in situ*. It is concluded that the features of microinvasive cancer of the cervix are distinctive and that they permit a positive differential diagnosis in 27 of 31 cases.

- 1888 STUDIES ON THE HISTOGENESIS OF EXPERIMENTALLY INDUCED BRAIN TUMORS: I. LIGHT MICROSCOPIC STUDIES. (Ger.) Warzok, R. (Med. Acad., Erfurt, Germany), G. Osski and R. Zabel-Langhennig. *Exp Path* 5:148-153, 1971.

Histogenesis of a methylnitrosourea (MNU)-induced brain tumor in a Hauben rat was studied by means of serial transplants of the tumor. A pea-sized tumor developed 137 days after a series of five i.p. injections of 20 mg/kg MNU. The tumor invaded the stem ganglia, the basal meninges and the osseous base of the skull, showing infiltrative growth along the blood vessels. In the transplant experiments, 0.5 mm portions of tumor were inoculated into the right cerebral hemisphere of four- to six-week old homologous Hauben rats. On the death of the animals, the procedure was repeated in the following generation. The primary tumor was transplanted to 224 rats through 40 generations. The latency period was 40 days following the first transplant and decreased to an average of  $11.5 \pm 1.5$  days in the 11th transplant generation. Intracerebral tumors developed at the transplant sites in 89% of treated rats. Morphologic features of the primary and transplanted tumors included medium-sized mononuclear cells with diffuse boundaries, eosinophilic cytoplasm, infiltrative growth, and areas comprised of cells characteristic of oligodendroglioma. Cell vacuolation was not a generalized occurrence. Vacuolated cells were absent in certain transplant generations but were found in others.

- 1889 MORPHOLOGIC STUDIES PERFORMED ON EXPERIMENTAL FUNCTIONAL METAPLASIA AND PRECANCEROUS METAPLASIA IN MAN. (Rum.) Caluser, I. (Med. Pharm. Inst. Cluj, Rumania) and V. Ticlete. *Clujul Med* 44(1):139-145, 1971.

Morphologic alterations occurring in non-neoplastic and pretumoral metaplasia were studied in dogs and in biopsy material of precancerous cervical and laryngeal epithelium specimens collected from 465 patients. Non-neoplastic metaplasia in dogs was produced by autologous ileal fragment grafts made on the bladder; the animals were sacrificed 1, 2, 3, 4, 5, 6, 8, and 12 months after surgery. Intense epithelial proliferation in both the host and graft tissue was observed one month post-surgery, and atrophic alterations of the ileal mucosa were observed at the end of the second month following surgery. Typical epithelium formed under physiological conditions of the host organ was considered to be a regenerative rather than a metaplastic process. Altered conditions occurring either in the host or in the graft at the surgical site led to atypical or dys-

trophic metaplasia in certain animals. An important morphologic feature of the biopsy material was the presence of circumscribed cell formations with dense cytoplasm which sometimes were keratinized. A lengthening and hyperchromia of the mucosal basal cell nuclei, referred to as "cellular unrest", constituted another feature of the specimens studied. No qualitative or quantitative respiratory enzyme activity alterations were ascertained histochemically as compared to normal mucosa samples. Cytoplasmic organelle patterns appeared to be normal except for minor decreases in mitochondrial formations. The lack of atypical mitoses and nuclear forms precluded the expression of malignancy in the given samples.

- 1890 MALIGNANT TRANSFORMATION OF TERATOMATOUS FORMATIONS OF THE MEDIASTINUM. (Rus.) Seleznev, Ye. K. (I. P. Pavlov 1st Leningrad Med. Inst., USSR) and A. S. Ignat'yev. *Klin Khir* 8:23-25, 1971.

Observations of 26 cases of teratomatous dermoid formations were made in 14-20% of patients operated on for mediastinal tumor. Histologic investigations revealed dermoid cysts in 12 patients and teratoma in 14 cases (16 males and ten females). Most of the patients were in late stages of teratomatous development. The tumors were located in the superior and central mediastinum in 16 cases, and in the inferior mediastinum in ten cases. Teratomatous formations were found in the anterior mediastinum in 21 cases, and in the posterior part in five cases. Malignant transformation of the tumors was observed in six of 26 cases. Asymptomatic tumors were revealed incidentally in the course of routine X-ray examinations in five cases. Recurrence of the teratomatous formation with metastases and malignant transformation was observed in one case.

- 1891 A CLASSIFICATION OF NUCLEAR ABERRATION IN RELATION TO MALIGNANCY ASSOCIATED CHANGES (MAC). (E.) Finch, R. R. (Sch. Dent., U. Louisville, Ky.). *Acta Cytol* 15(6):553-558, 1971.

Buccal smears taken from normal patients or those who had metastatic or nonmetastatic cancer were studied and classified into five groups according to malignancy associated changes (MAC) as previously described. An increase in the frequency of abnormal nuclei was observed in the cancer patients. Within the cancer series, morphological characteristics of MAC were variable over a two day period. Statistical analyses indicated that cells showing complete MAC (type 5) were more significantly associated with a diagnosis of malignancy ( $p = 0.0014$ ) than were cells showing incomplete MAC (type 4;  $p = 0.048$ ). An analysis of the absolute diagnostic accuracy of these classifications could not be made.

- 1892 PATHOLOGIC ANATOMY OF GASTRIC CANCER AND OF ITS PRECANCEROUS LESIONS IN CHILEANS. (Sp.) Zaldivar, R. (Inst. Pathol. Anatomy, Santiago, Chile). *Gaceta Med Mex* 102(5):511-520, 1971.



Anatomical and pathological data on 91 gastric cancer patients (65 males and 26 females) following necropsy, including a review of precancerous lesions among Chileans, are presented. Major incidence of gastric cancer was observed among the 50-60- and 60-70 yr age groups. Of 91 neoplasms, 89 were carcinomas, one was a leiomyosarcoma and one was a lymphosarcoma; of 89 carcinomas 79 developed metastases. Carcinomas of the Ist, IInd, IIIRD and IVth degrees (according to Broder's classification) developed metastases with an incidence of 14.2, 85.0, 81.2 and 90.0%, resp., suggesting an inverse relationship between the differentiation of cells and the growth of metastases. One observed lesion appeared as a deep penetrating benign peptic ulcer with cancerous features at its boundaries. However, certain areas lacking glandular structures and with giant hyperchromatic nuclei could be observed. In a review of epidemiologic studies, the frequency of malignant transformation of ulcer was found to be 3-5% in Chile among gastrectomized patients. Evidence for a 30% incidence of gastric ulcer among the gastric cancer patients was found in Santiago and Valparaiso. No systematic data on the association between chronic gastritis and gastric cancer in Chile was available. Reference is made to 61 autopsies with chronic gastritis where the pyloric antrum, known to constitute the prevalent site of gastric cancer, was the site of the lesion in 60% of the specimens examined.

1893 ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS AND SOLUBLE PROTEINS OF THE MOUSE LIVER IN THE PROCESS OF EXPERIMENTAL HEPATOCARCINOGENESIS. (Rus.) Potapenkova, L. S. (USSR Ministry Publ. Hlth., Leningrad). *Vop Onkol* 17(9):65-70, 1971.

Electrophoretic mobility (agar-agar) of the water soluble serum, liver and hepatoma proteins of C3HA mice was studied during various stages of ortho-aminoazotoluene (OAAAT)-induced hepatocarcinogenesis. The carcinogen was added to the daily diet in 2 mg/mouse/day doses for 100 days. Six serum protein fractions, the first three corresponding to albumins and alpha globulins, the fourth and fifth corresponding to beta globulins and the sixth corresponding to gamma globulins were followed before the beginning and throughout the duration of the feeding experiment. Normal liver proteins presented eight fractions two of which traveled towards the anode; the same fractions were identified during the late stages of hepatocarcinogenesis also. The amount of liver protein fractions corresponding to alpha-globulins (normal 14-18%) decreased after 15 days, increased suddenly to 21-24% after 30 days of treatment, and dropped to 10% at the end of the feeding experiment. These fractions reached 23-29% in both hepatoma and hepatoma bearing livers. Of the liver protein fractions corresponding to the beta-globulins, fraction IV increased from 15.5 to 25% after 15 days and decreased after 30 days of treatment. Fraction V increased from 18.8 to 28.8% after 60 to 100 days of treatment in the liver and decreased to 6.8% in the hepatoma tissue. The electrophoretic dynamics of the liver protein frac-

tions seem to reflect two basic processes occurring during the process of hepatocarcinogenesis, one related to electrochemical alterations of the protein molecule as affected by the action of the carcinogen and another resulting from compensatory protein synthesis processes due to adaptation tendencies of the organism.

1894 AN ONCOGENIC INFECTIOUS NUCLEOPROTEIN AND STAGES OF CANCERIZATION OF THE UTERINE CERVIX. (Ger.) Eschbach, W. (Inst. Cancer Research, German Acad. Sci., Berlin). *Arch Geschwulstforsch* 37(4):352-367, 1971.

The dynamics of malignant transformation of the human uterine cervix were studied in human embryo kidney cell (HEK) cultures *in vitro*. The 402 cervical cancer cases included: 114 first and second degree dysplasias; 33 third-degree dysplasias; 65 carcinomas *in situ*; 90 carcinomas *in situ* and in the beginning stage of stromal invasion; 49 microcarcinomas; and 51 common invasive cancers. Inoculation of HEK cultures with cell-free extracts from first to third degree dysplasias, carcinomas *in situ* or early cervical carcinomas always resulted in a specific cytopathogenic effect following a one- to three-day latency period. Appearance of focal lesions within the dense cell layer constituted the first symptom and was followed by nuclear atypia and an evident vacuolation of the cytoplasm. The range of alterations observed within the cell culture through its total deterioration is described. The presence of a self-reproducing factor could be detected in cultures inoculated with cell-free extracts from early stages of a cervical cancer specimen. Propagation of this factor was confirmed using a 1:4 dilution factor and titration data. Reference is made to previous work which showed this factor to be an oncogenic nucleoprotein. The presence of this nucleoprotein was found regularly during early precancerous stages by homologous serum neutralization tests; the factor could not be detected in samples from common invasive cancer. This nucleoprotein is considered to be the primary pathogenic factor of carcinogenesis of the uterine cervix.

1895 TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS. (E.) Folkman, J. (Harvard Med. Sch., Boston, Mass.). *New Eng J Med* 285(21):1182-1186, 1971.

The isolation of a factor from human and animal tumors mitogenic to endothelial cells and stimulating the formation of new capillaries in animals is studied. This factor is designated tumor angiogenesis factor (TAF). It was first isolated in the Sephadex fraction II of the eluate from both solid and ascites tumor cells. It has a molecular weight of approximately 100,000, a lipid component which reduces angiogenesis activity, and can react in the presence of steroids. TAF does not produce a permanent change in capillary endothelial cells; it is not species specific, since it is formed in the tu-

mors of human adults and children and in mice and can cause neovascularization in the healthy tissues of rats, mice, and rabbits regardless of host origin. Immunization against TAF may be of future use in the treatment of tumors. For example, it is possible that metastases will not originate from non-vascularized tumors. It is also probable that tiny unvascularized tumors may be far more vulnerable to chemotherapy and to the host's own immunologic processes than are large tumor masses. Since the growth of solid neoplasms is always accompanied by neovascularization, the author feels it imperative to investigate the role of TAF in the behavior of tumor cell proliferation more thoroughly.

- 1896 PROLIFERATIVE ENDOMETRIAL RESPONSE TO THECA-GRANULOSA CELL TUMORS. (E.) Gusberg, S. B. (Mount Sinai Hosp., New York, N.Y.) and P. Kardon. *Amer J Obstet Gynec* 111(5):633-643, 1971.

A study of proliferative endometrial changes in patients with "feminizing" ovarian tumors was undertaken in an effort to clarify the nature of these changes in respect to cancer precursors, such as cancer in situ, invasive adenocarcinoma and adenomatous hyperplasia. The historical data and histology of the endometrium and ovarian tumors of 115 patients with so-called feminizing ovarian tumors were recorded. Cancer precursors were noted in 43 per cent and carcinoma in 21 per cent. No firm conclusions could be drawn about the carcinogenic activity of estrogen in human beings from this data since problems of selection and other endocrinopathies may have been involved.

- 1897 NEUROHISTOLOGIC DEVELOPMENT OF SKIN EPITHELIOMAS. (It.) Amerio, P. L. (Catholic U. Rome, Italy), F. Ormea and L. Rusciani. *Ann Ital Dermatol Clin Sperim* 24(2):181-200, 1970.
- 1898 ULTRASTRUCTURAL DEVELOPMENT OF SKIN EPITHELIOMAS. (It.) Bossi, G. (Catholic U. Rome, Italy), A. Garcovich and F. Ormea. *Ann Ital Derm Clin Sperim* 24(2):161-180, 1970.
- 1899 COMPARATIVE ROLE OF PNEUMOSCLEROSIS OF DIFFERENT ORIGIN IN THE DEVELOPMENT OF LUNG CANCER. (Rus.) Braude, V. I. (Moscow Res. Inst. Tuberc., USSR). *Sovet Med* 34(6):99-103, 1971.
- 1900 DNA CONTENT IN PRENEOPLASTIC CONDITIONS OF SKIN. (Ger.) Ehlers, G. (Technical U. Munich, Germany). *Fortschr Med* 89(27):1042-1043, 1971.
- 1901 HISTAMINE METABOLISM IN PRETUMORAL DISEASES OF THE STOMACH. (Rus.) Eydel'man, F. M. (Inst. Onkol. Probl., Ukrainian Acad. Sci., Kiev., USSR). *Vrach Delo* 8:94-98, 1971.
- 1902 MALIGNANT LYMPHOGANULOMA WITH A PRIMARY CUTANEOUS SITE. (It.) Rabbiosi, G. (Pavia

U., Inst. Clin. Dermatol., Italy), G. Casirola, and G. Santagati. *Chron Derm* 1(5-6):271-283, 1970.

- 1903 ULTRASTRUCTURAL FEATURES OF THE EARLY PROLIFERATING CELLS INVOLVED IN HEMPOIETIC COLONY FORMATION. (E.) Degowin, R. L. (Dept. Med., U. Iowa, Iowa City), J. C. Hoak and S. H. Miller. *Radiat Res* 48(3):495-507, 1971.
- 1904 ADENYL CYCLASE, PHOSPHODIESTERASE AND CYCLIC AMP DEPENDENT PROTEIN KINASE OF MALIGNANT GLIAL CELLS IN CULTURE. (E.) Perkins, J. P. (U. Colorado Med. Sch., Denver), E. H. Macintyre, W. D. Riley and R. B. Clark. *Life Sci* 10(18):1069-1080, 1971.
- 1905 GROWTH AND DIFFERENTIATION OF A TRANSPLANTABLE PLASMACYTOMA: I. PATTERNS OF WEIGHT INCREASE AND PARAPROTEINEMIA. (E.) Huemer, R. P. (VA Hosp., Sepulveda, Calif.) and C. Bickert. *Oncology* 25(5):439-445, 1971.
- 1906 KERATOACANTHOMA: DEVELOPMENT INTO SQUAMOUS CELL EPITHELIOMA. (It.) Scarpa, C. (Derm. Clin., Rome U., Italy). *G Ital Derm* 46(112):365-368, 1971.
- 1907 A CASE OF GASTRIC CARCINOMA ASSOCIATED WITH LYMPHOID LEUKEMIA: PATHOGENESIS. (It.) Renzi, G. (Civic Hosp., Rimini, Italy). *Riforma Med* 85(18):485-489, 1971.
- 1908 CONDITIONS OF MORPHOLOGICAL APPEARANCE AND DEVELOPMENTAL POTENTIAL OF PRECANCEROUS LESIONS OF THE LARYNX. (Fr.) Derout, J. (Boucicaut Hosp., Paris, France), J. de Brux and J. Leroux-Robert. *J Franc Otorhinolaryng* 20(9):1057-1063, 1971.
- 1909 ABERRANT SEX RATIOS AMONG THE TUMOROUS-HEAD STRAINS OF *DROSOPHILA MELANOGASTER*. (E.) Kuhn, D. T. (Dept. Biol., Creighton U., Omaha, Nebraska). *Genetics* 69:467-478, 1971.
- 1910 DISSOCIATION OF ERYTHROBLASTIC AND MYELOBLASTIC PROLIFERATION IN ERYTHROLEUKEMIA. (E.) Roloff, J. N. (U. Missouri Sch. Med., Columbia) and J. N. Lukens. *Amer J Dis Child* 123:11-13, 1972.
- 1911 THE QUESTION OF RECURRENCE AND MALIGNANT TRANSFORMATION IN KERATOACANTHOMA (MOLLUSCUM SEBACEUM). (E.) El-Domeiri, A. (Fac. Med., Al-Azhar U., Cairo, Egypt). *J Egyptian Med Ass* 54(1):68-73, 1971.



1912 THE SO-CALLED EPITHELOID CELLS IN GLOMUS  
TUMORS AND ARTHEIO-VEINUS EPITHELOID CELL  
ANASTOMOSES, HISTOGENESIS, ULTRASTRUCTURE AND FUNC-  
TIONAL MEANING. (Ger.) Lüders, G. (Derm. Clin.,  
U. Tübingen, Germany), W. Schlote and M. Reinhard.  
*Medizin Welt* 22(36):1374-1378, 1971.

1913 KARYOLOGY STUDIES ON PRIMARY NEOPLASMS OF  
THE CHINESE HAMSTER. (Rus.) Pogonyants,  
Ye. Ye. (U.S.S.R. Acad. Med. Sci, Moscow), O. I.  
Sokova and E. T. Bruyako. *Vop Onkol* 17(8):61-67,  
1971.

See also:

- \* (Rev): 1507, 1512, 1514, 1515, 1523, 1528
- \* (Chem): 1552, 1560, 1606, 1609, 1629
- \* (Phys): 1658
- \* (Viral): 1764
- \* (Epid-Biom): 1925

- 1914 LEUKEMIAS IN THE CRACOW REGION IN THE YEARS 1961-1968. (E.) Janicki, K. (Med. Acad., Cracow, Poland). *Acta Med Pol* 12(3):427-442, 1971.

Statistical materials from hospital record are used to determine the morbidity of leukemias in the Cracow province. In the period 1960-1968 a total of 1,045 patients were diagnosed as having leukemia. Unification of the nomenclature was established for this report so that cases with different names but similar clinical characteristics could be included in the same group. The frequency of leukemia occurrence was defined on the basis of the following indexes: 1) the overall morbidity in Cracow for all types of leukemia; 2) the morbidity in Cracow for each of the three types of leukemia; 3) the morbidity of all three types of leukemia in Cracow for the following population groups: a) men and women; b) inhabitants of towns and rural areas; c) age groupings of children, middle aged and older persons; d) morbidity divided into clinical types and population groups within the 18 administrative units in Cracow. Overall morbidity amounted to 4.95/100,000 inhabitants/yr. A marked difference in the morbidity rate is found in the clinical types of leukemia with the highest morbidity rate occurring among cases of acute leukemia and the lowest rate in the chronic granulocytic leukemia group. Morbidity in different population groups shows indexes higher than in previous studies completed in this region. There was a higher morbidity index for men than for women, with a striking increase found in persons over the age of 45 years. Results presented are considered preliminary and have a descriptive character; detailed analyses are in process with the purpose of elucidating the relations between causal environmental factors and morbidity.

- 1915 RELATIONSHIP OF CORONARY HEART DISEASE TO MALIGNANT DISEASE: AN AUTOPSY STUDY. (E.) Mänttönen, M. (Dept. Pathol., U. Turku, Finland) and M. Nuutila. *Pathology* 3(4):279-283, 1971.

In 643 autopsies performed in cases over the age of 30 yrs, 244 subjects were found to have coronary heart disease and 399 were not. In both groups the incidence of malignant disease (this included carcinoma, sarcoma, malignant lymphoma and leukemia) was statistically evaluated. A negative correlation was found between severe atherosclerosis and coronary atherosclerosis on the one hand and all carcinomas on the other. With a negative association prevailing between heart disease and neoplasms it was suggested that the malignant tissue should be classified according to type in future to determine if data would continue to indicate high incidence of neoplasm in patients without severe generalized and coronary atherosclerosis.

- 1916 CHILDHOOD LEUKAEMIA IN SCOTLAND, 1939-68. (E.) Hems, G. (Med. Sch., U. Aberdeen, Scotland) and A. Stuart. *Scot Med* 17(1):13-17, 1972.

Leukemia mortality rates of children in Scotland for 1939-1968 are reported. Data was obtained from the Registrar General's Annual Reports for Scotland; in the 30-yr period from 1939 to 1968 978 children aged 0-14 years were reported to have died from leukemia (561 male and 417 female). Mortality rates were found to increase from 1939 until the mid-1950's and then to decline for all leukemias; a similar trend was seen in England and Wales, in the United States and in Norway. The mortality rates for lymphatic leukemia showed a three-fold increase in the period studied; myeloid or monocytic leukemia rates were seen to increase by two and one-half times for females aged 0-14 years but remained fairly constant for males. For 271 leukemias in which the time of onset of symptoms was recorded (excluding 35 cases of myeloid or monocytic leukemia), median survival time was two months in the 1940's, increased in the 1950's, and was six months during 1960-1968. Mortality rates for ten regions of Scotland were not found to be significantly different, and no evidence of seasonal variation was seen for the monthly distribution of onset of leukemia.

- 1917 CANCER MORTALITY-UNITED STATES, CANADA, AND WESTERN EUROPE. (E.) Anonymous. *Statistical Bull* 52:6-9, 1971.

Mortality from neoplasms of males and females aged 45-74 in the United States, Canada and selected European countries was analyzed according to age, sex and type of cancer for 1966-67. Standardized mortality rates from cancer of all sites for white males aged 45-74 varied from 410.9/100,000 in Canada to 514.4/100,000 in the industrialized European countries. The United States death rate was 427.5/100,000 for white males and 580/100,000 for nonwhite males. Mortality rates for white females ranged from 270.0/100,000 in Southwest Europe to 324.4/100,000 in the industrialized European countries. Death rates from cancer of all sites increased with age, doubling each ten-yr period for males in the United States and Canada; increases for females were not as sharp. The highest death rate according to site in males was for cancer of the respiratory tract. Twice as many men as women died of stomach cancer. The death rate for intestinal cancer was about the same for both sexes. The breast was the primary site of cancer among women. Breast cancer caused a higher mortality in white than non-white women.

- 1918 CRYPTOGENIC METASTASES IN UGANDA AFRICANS. (E.) Templeton, A. C. (Dept. Path., Makerere U., Kampala, Uganda), M. S. R. Hutt and O. G. Dodge. *J Bone Joint Surg* 54B(1):125-129, 1972.

Results of a study on 175 malignant bone tumors from biopsy specimens at the Department of Pathology at Makerere University College in Uganda during the years 1964 to 1968 are presented. Bone tumors were divided into three groups: 1) lymphoreticular tumors; 2) secondary carcinoma; and 3) primary tumors of bone and cartilage, including osteosarcoma, chondrosarcoma, malignant giant-cell tumor, chordoma, and



round-cell bone tumor. Cases in which the primary tumor was found prior to bone biopsy were excluded, as were tumors of the maxilla and mandible and benign bone tumors. The thyroid was found to be the most common source of metastatic skeletal carcinoma (11 of 52 cases); it was postulated that this was due to the high incidence of endemic goiter in the patients studied. Of 11 patients with occult primary thyroid cancer nine were female. Hepatocellular carcinoma was found to be a common tumor; carcinoma of the bronchus and kidney were uncommon. Burkitt's tumor was most commonly found in the jaw. Lymphoma was mainly found in younger people, 0 to 19 yr of age. Most primary bone tumors were found around the knee; tumors of the skull, vertebrae, and head of femur were more likely found to be secondary.

- 1919 EPIDEMIOLOGICAL ASPECTS OF GALLBLADDER AND BILIARY TRACT NEOPLASM. (E.) Hart, J. (Tel Hashomer. Govt. Hosp., Tel Aviv, Israel), M. Shani and B. Modan. *Amer J Public Hlth* 62(1):36-39, 1972.

Epidemiological data regarding gallbladder and biliary tract tumors were collected from diagnostic listings and Cancer Registry records in Israel for the period 1960-1965. Cases were divided by diagnostic criteria into two groups: definite and probable. It was found that there were few cases under the age of 35, while more than 50% of the cases occurred at the age of 65 or over. The male-female ratio was about 1:5 for all age groups. Incidence of gallbladder cancer was more prevalent in women who had migrated from Europe than in women who had migrated from Asia or Africa; no such correlation was found in men. At least 50% of the patients with gallbladder cancer had had biliary disease history, such as gallstones, for at least five years prior to diagnosis of the gallbladder cancer. Findings seem to support the hypothesis that cholelithiasis plays a role in the etiology of gallbladder cancer; this should be confirmed through prospective studies.

- 1920 INCREASING INCIDENCE AND DECREASING MORTALITY RATES FOR BREAST CANCER. (E.) Cutler, S. J. (Natl. Cancer Inst., Bethesda, Md.), B. Christine and T. H. C. Barclay. *Cancer* 28(6):1376-1380, 1971.

Two geographic areas with good cancer reporting systems (Connecticut, U.S.A. and Saskatchewan, Canada) were observed to determine contrasting trends between breast cancer incidence and mortality. It was found that the incidence of breast cancer has increased in each of the four 10-year age groups between the ages 35 and 75, while the rate has been decreasing among women under the age of 35. In spite of the increased incidence in some groups the mortality rate has decreased for both localized and regional mammary disease. Such improvement in survival, though, cannot be definitely attributed to improved diagnostic techniques, better treatment strategies, or a shift in the spectrum of disease states.

- 1921 MORTALITY TRENDS IN CARCINOMA OF THE CERVIX UTERI. (E.) Campos, J. L. (Dept. Radiol., U. Michigan, Ann Arbor). *J Chron Dis* 24(1):701-709, 1971.

Cancer mortality trend of stages I through IV of carcinoma of the cervix uteri is discussed. Mathematical analyses are performed on data from 1202 staged cases of cervical cancer in a 23-year span to determine the number of deaths occurring over a five-year period. Of all cancer deaths from stage IV 75% occurred during the first post treatment year while the remaining deaths occurred by the third post treatment year. One half of the deaths in stage III occurred during the first year of treatment; another 25% occurred during the second year. Mortality was 25% and 17% in stage II and stage I, respectively, during the first year of treatment but rose sharply thereafter, until 90% of all cancer deaths had occurred in these two stages by the fourth year post treatment. Such data suggest that the stages may be expressed in terms of an exponential function. It is noted that cases of cervical carcinoma that are not cured are not grossly affected by treatment; despite great improvements in the five-year survival rate the sequence of death has not shown major change.

- 1922 THE PILL, ESTROGENS, AND THE BREAST: EPIDEMIOLOGIC ASPECTS. (E.) Arthes, F. G. (Second Natl. Conference Breast Cancer, Los Angeles, Calif.), P. E. Sartwell and E. F. Lewison. *Cancer* 28(6):1391-1394, 1971.

A preliminary study of 283 cases of breast cancer and 585 controls provides no evidence to associate administration of female hormones with the development of breast cancer. This study is based on drug products used as related to age, race, marital status, number of live births, menopausal age, and socio-economic level. The data relate chiefly to postmenopausal use of estrogens and not to oral contraceptives.

- 1923 TUBERCULIN ALLERGY AND CANCER RISK. (E.) Magnus, K. (Cancer Registry of Norway) and O. Horwitz. *J Chron Dis* 24(10):635-641, 1971.

Results of 12-yr epidemiologic study in Denmark correlating the tuberculin reaction with cancer incidence are given. The population studied comprised 425,532 persons with a negative history for tuberculous or previous BCG vaccination. All subjects had been given a single intradermal tuberculin reaction test. In the present study, the size of the tuberculin reaction was correlated with the risk of developing malignant disease. No differences were detected between the 2,661 dying of cancer during the 12-yr period and the remaining population with respect to the prevalence of tuberculin reactors and the mean size of the reactions among those with a positive tuberculin test.

- 1924 INTERACTION BETWEEN ABO AND RHESUS BLOOD GROUPS, THE SITE OF ORIGIN OF GASTRIC CANCERS, AND THE AGE AND SEX OF THE PATIENT. (E.) Glover, G. A. (Radcliffe Infirm., Oxford, England), E. G. Cantrell, R. Doll and R. Peto. *Gut* 12:570-573, 1971.

A study of 1,680 patients treated for gastric cancer was carried out to determine the relationship between ABO and Rhesus blood groups, the site of origin of gastric cancers and the age and sex of the patient. The mean age of the patients studied was 61.7 years. Male predominance in gastric cancer occurrence was noted up until the age of 60 years; males also predominated in cancers of the proximal and middle third of the stomach. Blood group A patients showed a greater frequency of gastric cancer than blood group O; there were 516 O type patients and 569 A type patients. The relative risk of cancer in group A patients was 16% greater than in O patients. No correlation was found between either ABO or Rhesus blood groups and site of origin of the tumor within the stomach or with the age or sex of the patient.

- 1925 OPISTHORCHOSIS AND LIVER NEOPLASIA IN THE KHANTY-MANSIYSK DISTRICT. (Rus.) Shayn, A. A. (Tyumen' Med. Inst., USSR). *Vop Onkol* 17(6): 34-38, 1971.

The relationship between opisthorchiasis and incidence of liver neoplasia was studied by comparing epidemiology and morbidity of liver cancer data in the Khanty-Mansiysk national district of the Tyumen region between 1960 and 1969. The highest liver cancer incidence (50 per 100,000 population) was found in the city of Khanty-Mansiysk where opisthorchiasis was diagnosed in 43% of 76,022 subjects examined. A 27.6% incidence of opisthorchiasis was associated with a 36 per 100,000 population liver malignancy in the Khanty-Mansiysk district. The Oktyabr district showed a 46.2% incidence of opisthorchiasis and a 29.5 per 100,000 population incidence of liver malignancy, which was three times the total incidence of liver cancer throughout the Tyumen region, known as one of the most important areas for the occurrence of opisthorchiasis. This discrepancy was attributed to the diagnostic difficulties in determination of primary liver cancer. Among 11,366 nursery school children, 1.3% had opisthorchiasis; this increased to 19.5% among high school students and to 49.1% among technical college students. Liver cancer occurred mainly among adult and old-age patients, indicating that a long period of parasitic invasion is a requirement for primary cancer development. The parallelism between opisthorchiasis and incidence of liver neoplasia within the adult group indicates a possible role of opisthorchiasis in the pathogenesis of primary liver cancer.

- 1926 BREAST CANCER MORTALITY IN YUGOSLAVIA. (E.) Krajcinovic, S. (Sch. Med., U. Belgrade, Yugoslavia) and S. Ducic. *Arch Geschwulstforsch* 38(1): 34-39, 1971.

A constant increase in deaths from malignant neoplasms of all kinds occurred in Yugoslavia during 1958-1967. In women, the number has increased from 6,542 in 1958 to 8,345 in 1967, a 27.5% rise. Breast cancer ranked highest (15.4%), followed by cancer of the stomach (15.2%) and cancer of the uterus (15.1%). Deaths caused by all malignancies increased from 8.9% in 1958 to 11.7% in 1966, and 10.4% in 1967. A rapid increase in age-specific mortality rates was registered in patients from 35 to 44 years of age. Maximum values were registered in women from 75 to 84 years of age. Differences were found in the mortality rate among the Yugoslavian regions, ranging from 5.0/100,000 in Bosnia, Herzegovina, Macedonia and Montenegro, to 15.5 in Slovenia and 13.2 in Croatia. Reasons for this are not yet fully understood, but may involve the age structure of the populations, and the quality of registration of causes of death. The lowest mortality rate was noted in regions with lower percentages of population over 45 years of age. The mortality rates in Yugoslavia were compared with rates of various other European countries.

- 1927 MORBIDITY AND MORTALITY OF CANCER OF THE NASOPHARYNX IN TAIWAN. (E.) Lin, T. M. (Coll. Med., Natl. Taiwan U., Taipei), M. M. Hsu, K. P. Chen, T. C. Chiang, P. F. Jung and T. Hirayama. *Gann* 10:137-144, 1971.

A survey of nasopharyngeal cancer in Taiwan was conducted from 1966 to 1968. A total of 1,516 cases was studied; there were 401 fatal cases. The morbidity curve for nasopharyngeal cancer rises from the 15-19 year age group, peaks at 40-44 years of age, and forms a plateau until 60-64 years of age. A slight decrease in morbidity is observed over 65 years of age. The age-adjusted incidence rate for nasopharyngeal cancer was 5.20/100,000 population (7.06 for males and 3.09 for females). The age-adjusted death rate was 1.53/100,000 population (2.06 for males and 0.95 for females). Mortality rates presented according to occupation reveal significantly higher rates in persons in the salt production, national defense, public service and mining industries. In general, it was found that Chinese have a higher rate of nasopharyngeal cancer than other groups on Taiwan. Age-specific morbidity and mortality rates show that nasopharyngeal cancer tends to appear at an earlier age than most forms of cancer.

- 1928 SWEDISH PILOT STUDY ON LUNG CANCER AMONG MINE WORKERS. (Sw.) Axelsson, O. (Med. Clin., Orebro, Sweden), M. Rehn, H. Josefson and L. Sundell. *Läkartidningen*, 68(49):5687-5693.

A general survey of Swedish mines in 1969 revealed radon concentrations exceeding a recommended limit of 30 pC/liter in 22 of the 60 mines investigated. A retrospective study on lung cancer mortality among workers of Narka zinc mine (Sweden) during 1956-1970 was carried out based on statistical and other data. In taking the age distribution into account, the found and expected mortalities for mine workers (440) and nonminer male inhabitants of the community were



compared. Significant rise in the lung cancer mortality for the entire community was determined. Mine workers accounted for about 75% of the total lung cancer mortality. Mortality for miners was about 13 times higher than expected (27.5/10,000 against 2.1/10,000); lung cancer mortality for the entire community was about normal (6.3/10,000 against the expected value of 3.2/10,000). Three of the active miners who died from lung cancer were nonsmokers. While average exposure time was long (35 years) death occurred some years after retirement in a fairly high number of cases. Lung cancer was found in seven of 112 miners who worked for at least 10 years. In view of these facts, the presence of carcinogenic radiations in the mine primarily of radon and radon decay products (possibly in concentrations of about 200-300 pC/liter) in the period investigated, as well as other air-borne metal particles, Diesel-exhausts and oil vapors may be assumed.

cers of the stomach, colon, rectum, lung and breast were lower than or equal to those obtained in some countries known for low rates at these sites.

- 1931 CANCER IN CHIANG MAI, NORTH THAILAND: A RELATIVE FREQUENCY STUDY. (E.) Menakanit, W. (Chiang Mai Med. Sch., Thailand), C. S. Muir and D. K. Jain. *Brit J Cancer* 25(2):225-236, 1971.

A survey of 1877 cases of cancer diagnosed in northern Thailand is presented. The commonest sites for cancer in order of rank in males were: laryngeal-hypopharyngeal region (171 cases); penis (60 cases); stomach (53 cases); skin (53 cases). In females the most common sites were: cervix uteri (180 cases); breast (80 cases); skin (55 cases). Cancer rates by age, sex and relative frequency are detailed. There is a moderately high frequency of lip cancer in males and females; this elevated frequency is attributed to the chewing of betel quid and of Miang, a concoction of fermented boiled tea leaves. The overwhelming preponderance of hypopharyngeal and laryngeal cancers in males (18.4%) is related to keeyo smoking (keeyo is a type of local cigar); in females the frequency of laryngeal cancers is moderate (3.4%). Virtually all cancers of the hypopharynx and larynx seen in the Thai province of Chiang Mai have been fairly well-differentiated squamous carcinomas. Possible etiological factors have been indicated. The equal frequency of lung cancer in both sexes is an unusual finding, contrasting with the five-fold male preponderance for hypopharyngeal-laryngeal cancers.

- 1932 LEUKEMIA AND MULTIPLE MYELOMA IN FARMERS. (E.) Milham, S., Jr. (Washington State Dept. Social Hlth. Services, Olympia). *Amer J Epidemiol* 94(4):307-310, 1971.

Analysis of deaths from leukemia-lymphoma group cancers and occupation as stated on death certificates revealed a statistically significant association between farming occupations and death from leukemia and multiple myeloma. No such association was seen for Hodgkin's disease, reticulum cell sarcoma, or other lymphomas. The leukemia-farming association was strongest in men under age 60 with lymphatic and acute types of leukemia. Poultry farmers showed the highest proportionate case excess in the leukemia study. These findings are consistent with the hypothesis that agricultural environments contain agents which may cause leukemia.

- 1933 THE RISING INCIDENCE OF CARCINOMA OF THE PANCREAS: REAL OR APPARENT? (E.) Krain, L. S. (Los Angeles, Calif). *J Surg Oncol* 2(2):115-124, 1970.

- 1934 THE EXACTITUDE OF CAUSES OF DEATH: A COMPARISON OF AUTOPSY DIAGNOSES OF A SERIES OF

- 1929 LYMPHOMA IN OKINAWA. (E.) Oshiro, T. (Fukuoka Teishin Hosp., Japan), M. Maeshiro, T. Hiki, Y. Nohara and S. Hirata. *Gann* (10):249-255, 1971.

A total of 409 cases of microscopically diagnosed lymph node biopsy is reported. Malignant lymphoma accounts for about 20% of all cases, similar to findings from the Japanese mainland (Honshu). Nonspecific or reactive lesions, including cat-scratch disease, are 40%, which is about twice the incidence reported in Honshu. The male-female ratio is similar to those in Honshu and is greater than 2:1. Data (641 cases) collected on malignant lymphoma of the gastrointestinal tract in Okinawa from 1964-69 are summarized. Early cancer, confined to mucosa, was 10%, advanced cancer 85.4%, reticulum cell sarcoma 3.3% and leiomyosarcoma 1.3%. Reticulum cell sarcoma is the only lymphoma found in the stomach. Male-female ratio is 2:3, and most of the patients are beyond the age of 40 and clinically diagnosed as advanced carcinoma. A very high incidence (eight cases) of reactive lymphoreticular hyperplasia is present; the male female ratio is 3:5. The age distribution shows a greater incidence in the younger generation.

- 1930 MORTALITY FROM CANCER IN GREATER BOMBAY. (E.) Paymaster, J. C. (Tata Mem. Ctr., Bombay, India) and P. Gangadharan. *J Indian Med Ass* 57(2):63-69, 1971.

A survey of cancer mortality in Greater Bombay was made between 1964-67. Data were provided under two headings: 1) total deaths from all malignant neoplasms classified by sex and age; and 2) deaths classified under the World Health Organization Criteria. A total of 206,577 deaths was registered in Greater Bombay. The annual death rate was 1,050 per 100,000 population. Cancer was the sixth most common cause of death in males and seventh in females. The rate of mortality increased with age, peaking in the 75+ age group. The rate of increase in the different age groups for can-

MESOTHELIOMAS AND OTHER MALIGNANT LUNG TUMORS. (Fr.) Ducic, S. (Dept. Epid., McGill U., Montreal, Canada). *Canad J Public Health* 62(5):395-402, 1971.

1935 ESOPHAGEAL CANCER IN THE CASPIAN LITTORAL OF IRAN: INITIAL STUDIES. (E.) Kmet, J. (Internatl. Agency Res. Cancer, Lyon, France) and E. Mahboubi. *Science* 175(4024):846-853, 1972.

1936 CHRONIC MYELOCYTIC LEUKAEMIA IN AFRICAN CHILDREN. (E.) Lowe, R. F. (Harari Central Hosp., Salisbury, Rhodesia). *Trans Roy Soc Trop Med Hyg* 65(6):840-841, 1971.

1937 CARCINOMA OF THE STOMACH. (E.) Yamamoto, T. (Atomic Bomb Casualty Commission, Hiroshima, Japan). *Hum Path* 2(4):535-537, 1971.

1938 MALIGNANT TUMORS OF THE PHARYNX, TREATED AT THE INSTITUTE OF ONCOLOGY IN GLIWICE IN THE YEARS 1954-1963. (Pol.) Wieckowska, Z. (Inst. Oncol., Gliwice, Poland) and J. Swiatnicka. *Otolaryng Pol* 25(6):643-649, 1971.

1939 FAMILIAL NEUROBLASTOMA: REPORT OF A KINDRED WITH A HIGH INCIDENCE OF INFANTILE TUMORS. (E.) Hardy, P. C. (U. Minnesota Hosp., Minneapolis) and M. E. Nesbit, Jr. *J Pediat* 80(1):74-77, 1972.

1940 MATHEMATICAL METHODS IN THE EPIDEMIOLOGY OF MALIGNANT TUMORS. (Rus.) Dolgintsev, V. I. (USSR Acad. Med. Sci., Moscow). *Vop Onkol* 17(8):95-101, 1971.

1941 MEDICAL AND SOCIAL PROBLEMS IN EARLY DETECTION OF NEOPLASIA. SECOND PART: ORGANIZATION OF A CENTER FOR EARLY DETECTION OF NEOPLASIA OF FEMALE GENITALS. (It.) Mele, G. (G. Casati Reg. Hosp., Milan, Italy) and G. Cavasonza. *Atti Acad Med Lombarda* 24(4):425-430, 1969.

1942 THE PHILADELPHIA PULMONARY NEOPLASM RESEARCH PROJECT: BASIC RISK FACTORS OF LUNG CANCER IN OLDER MEN. (E.) Boucot, K. R. (Philadelphia Pulmonary Neoplasm Res. Project, Pa.), W. Weiss, H. Seidman, W. J. Carnahan and D. A. Cooper. *Amer J Epidemiol* 95(1):4-16, 1972.

1943 NEW INVESTIGATIONS ON ONCOLOGIC EPIDEMIOLOGY IN UPPER LOMBARDY. (It.) Sforza, M. (Ctr. Med. Stud., Milan, Italy) and E. Salmasso. *Atti Acad Med Lombarda* 24(2):190-192, 1969.

1944 OBSERVATIONS ON THE MORTALITY FROM CARCINOMA OF THE BREAST. (E.) Campos, J. L. (Dept. Radiol., U. Michigan, Ann Arbor). *Brit J Radiol* 45(529):31-38, 1972.

1945 CANCER IN NEUROLOGY. (Fr.) Collomb, H. (No affiliation), P.-L. Girard, M. Dumas and B. Courson. *Med Afrique Noire*, 18(6):539-555, 1971.

1946 MALIGNANT LUNG TUMORS IN PATIENTS BELOW 40 YEARS-OF-AGE. (Rus.) Aytakov, Z. H. (Khabarovsk Med. Inst., U.S.S.R.). *Klin Khir (Kiev)*, 8:65-66, 1971.

1947 CANCER IN CONNECTICUT, 1968. (E.) Christine, B. W. (Connecticut Tumor Registry), J. T. Flannery and P. D. Sullivan. *Connecticut Health Bull* 85(11):327-338, 1971.

See also:

- \* (Chem): 1583
- \* (Phys): 1657, 1660
- \* (Immun): 1833



1948 DETERMINATION OF THE NUMBER OF CELLULAR SITES FIXING CONCAVALIN A BY A CONSUMPTION TEST. (Fr.) Barra, Y. (Res. Service, CRACM, Marseilles, France), P. de Micco, M.-E. Lavy and G. Meyer. *C R Acad Sci (Paris)* 274(6):966-969, 1972.

The quantitative aspects of the interaction between cellular surface and a lectin were studied by a consumption test and the result was compared with results of similar studies using other methods. To a given quantity of the plant agglutinin Concanavalin A (27 mcg) in 1 ml solution, increasing amounts of transplantable hamster tumor first generation cells of the CT 54 strain (tumor induced by inoculation of newborn hamsters with a polyoma virus) were added until no more agglutination occurred. The test was performed in the presence of a phosphate buffer, at pH 7.4, under constant stirring at ambient temperature. Agglutination was determined in the supernatant liquid following centrifugation of the sample for five minutes. Agglutination was greatest with  $2 \times 10^6$  cells, thereafter it decreased linearly until it ceased when  $25 \times 10^6$  cells had been added. The Concanavalin A quantity representing  $23.5 \times 10^{13}$  molecules thus fixated  $25 \times 10^6$  cells which, taking into account cell diameter determined by electron microphotography, yields  $12 \times 10^3 \pm 2 \times 10^3$  sites per sq micron cellular surface capable of fixating Concanavaline A. The error of the method due to the imprecision of measuring cellular diameter is 16%. The number of cellular sites fixating Concanavaline A determined by the Inbar and Sachs method was estimated to be between  $6 \pm 2 \times 10^3$ /sq micron for normal cells and  $40 \pm 18 \times 10^3$ /sq micron for transformed cells. This difference was attributed to the fact that transformation is associated with an unmasking of sites which are hidden in normal cells.

1949 FETAL PATTERN OF ALDOLASE IN TRANSPLANTABLE HEPATOMAS. (E.) Schapira, F. (Nat'l. Inst. Hlth. Med. Res., Paris, France), A. Hatzfeld and M. D. Reuber. *Cancer Res* 31:1224-1230, 1971.

Activity of aldolases A (muscle), B (normal rat liver) and C (brain) were studied in three well-differentiated (122, 175 and 189) rat hepatomas and one poorly differentiated (178) hepatoma, as well as in normal and fetal rat liver. Enzyme activity was determined colorimetrically using either fructose diphosphate (FDP) or fructose-1-phosphate (F1P) as substrate. Aldolase A, which acts primarily on FDP, produces an FDP/F1P activity ratio of  $>50$ . Aldolase C gives an FDP/F1P ratio of five to eight, while that of type B is one. Slow-growing hepatomas had an aldolase activity ratio very close to normal ( $1.76 \pm 0.08$ ) whereas the poorly-differentiated hepatoma showed a ratio of  $32.2 \pm 2.3$ . Electrophoresis showed an abnormal isozyme pattern in the fast-growing hepatoma. Electrophoretic patterns of slowly growing hepatomas were close to that of normal liver. Immunologic studies indicated that: 1) the fast-growing hepatoma contains practically no normal liver aldolase B but does have types A and C; and 2) the slow-growing hepatomas contain aldolases A and B. Since aldolases A and C are found in fetal

tissue, the results were interpreted as supporting evidence for the existence of "derepression" of fetal forms of enzymes in hepatomas.

1950 CHROMOSOMES IN PREINVASIVE, MICROINVASIVE AND INVASIVE CERVICAL CARCINOMA. (E.) Granberg, I. (Inst. Path. Genet., U. Lund, Stockholm, Sweden). *Hereditas* 68(21):165-218, 1971.

A chromosome study was performed on 47 patients with cervical carcinoma. The patients were divided into three groups: 1) those suffering from marked dysplasia and carcinoma *in situ* (CIS); 2) those with CIS and microinvasion; and 3) those with invasive squamous carcinoma. Biopsies of affected tissues indicated that the diploid count was most common (70%) in marked squamous dysplasia and CIS; no gross abnormalities were found except for a few groups of cells exhibiting hypertriploid and hypotetraploid chromosome counts. Major chromosomal deviations were found in the A, C and D chromosomes, with alterations occurring occasionally in groups B, E, F and G. In CIS and microinvasive carcinoma, however, the counts in the hypo- and hyperdiploid range were more common (60%); there was also a significant shift from the tetraploid to the triploid region, with most counts dispersed throughout the triploid region (32%). Major chromosomal deviations were similar to those mentioned previously. In the invasive tumors, the B, C, D and G chromosomes had the highest frequencies of deviations; furthermore, the proportion of tumors with gains or losses in these groups increased as the disease progressed. Other chromosomes were also involved, but usually these exhibited no clear deviation trend. The present study shows that development and progression of malignancy in squamous cervical epithelium is accompanied by chromosomal changes. These changes qualitatively involve the same pattern at all levels of malignant development. The karyotype deviations support the hypothesis that chromosome changes tend to increase in frequency and severity with increasing degree of malignancy, from CIS to the microinvasive stage to invasive carcinoma.

1951 REGRESSION OF SPONTANEOUS MAMMARY TUMORS IN RATS BY ERGOT DRUGS. (E.) Quadri, S. K. (Dept. Physiol., Michigan State U., East Lansing) and J. Meites. *Proc Soc Exp Biol Med* 138(3):999-1001, 1971.

The inhibition of growth of spontaneous mammary tumors (singly occurring fibroadenomas) by ergocornine methane sulfonate (ERG) and 2-Br- $\alpha$ -ergokryptine (ERK) is reported. Sprague Dawley rats with single spontaneous mammary tumors were randomly divided into one control group, four groups given ERG and four groups given ERK. The drugs were injected daily i.p. in doses of 0.05, 0.10, 0.20, or 0.40 mg/100g of body weight in a solution containing 96% physiological saline and 4% ethanol of 70% strength. Control rats were injected daily only with the saline-ethanol vehicle. All doses induced marked regression of mammary tumor diameter during a four week treatment period. Tumor inhibition was

seen to continue for up to one week following a discontinuance of drug injection. During the test period tumors decreased from 2.81 cm to 1.54 cm in diameter with ERG and ERK treatment. This was in marked contrast to the gain in tumor size within the control group animals where tumors increased from 3.81 cm to 3.91 cm in diameter. Upon termination of the treatment tumor growth in the test animals resumed and proceeded at the same rate as in controls. The study indicated that: 1) ERG and ERK are almost equally effective in decreasing tumor size; 2) greater tumor inhibition was seen in smaller than in larger tumors; and 3) growth regression is probably the result of a depression of pituitary prolactin by ERG and ERK.

1952 G-6-PD AND PGM PHENOTYPES OF 16 CONTINUOUS HUMAN TUMOR CELL LINES: EVIDENCE AGAINST CROSS-CONTAMINATION AND CONTAMINATION BY HeLa CELLS. (E.) Beckman, G. (Dept. Clin. Bacteriol., U. Umea, Sweden), L. Beckman, J. Ponten and B. Westermark. *Hum Hered* 21:238-241, 1971.

Sixteen permanent human cell lines (13 derived from gliomas, two derived from osteosarcomas, and one derived from a synovial sarcoma) were analyzed for the presence of glucose-6-phosphate dehydrogenase (G-6-PD) and the phosphoglucomutase phenotypes PGM<sub>1</sub> and PGM<sub>3</sub>. Extracts of the HeLa, KB and WISH cell lines were used as reference samples for the G-6-PD variant A and red cell hemolysates from Caucasians for the G-6-PD variant B. Using gel electrophoresis it was found that the G-6-PD A variant was absent from all 16 cell lines, while the PGM<sub>1</sub> and PGM<sub>3</sub> phenotypes were present in all 16 lines. There was apparently no relationship between enzyme phenotypes and the length of time cells were cultured, thus confirming an explanation of phenotypic similarities between classical cell lines in terms of mutation and subsequent selection.

1953 HEPATITIS-ASSOCIATED ANTIGEN AND HEPATOMA IN THE U.S. (E.) Alpert, E. (Harvard Med. Sch., Massachusetts Gen. Hosp., Boston, Mass.). K. J. Isselbacher. *Lancet* (7733):1087, 1971.

Fifty-one patients with histologically confirmed hepatomas were surveyed by modified counter immunoelectrodifusion; hepatitis-associated antigen (H.A.A.) was found in only three patients who were born or raised outside of the U.S. The lack of H.A.A. in the remaining 48 patients who were born or raised in the U.S. suggests that H.A.A. is not related to hepatoma in the U.S.

1954 ENDOMETRIAL CARCINOMA RECURRING AFTER HISTERECTOMY: A STUDY OF 64 CASES, WITH OBSERVATIONS ON EFFECTIVE TREATMENT MODALITIES AND IMPLICATIONS FOR ALTERATION OF PRIMARY THERAPY. (E.)

Long, R. T. L. (Ellis Fischel St. Cancer Hosp. Columbia, Mo.), J. M. Sala and J. S. Spratt. *Cancer* 29(2): 318-321, 1972.

Sixty-four patients with proved postoperative recurrent endometrial carcinoma are studied and the incidence loci of recurrence, and methods of treatment are reviewed. Seventy-five percent of the cases which were studied showed recurrences in the vagina, pelvis or surgical wound; eighty percent of the recurrences appeared within five years. Among recurrences seen, untreated patients and those undergoing exenteration did poorly. The highest survival rate was obtained in patients that received transvaginal radiotherapy. Patients that underwent radiotherapy for disease recurrence or persistence following subtotal hysterectomy had excellent survival rates when combinations of radium and external radiotherapy were employed. Little correlation was noted between the grade of the tumor and survival except for the undifferentiated lesions. The prevention of implantation by tumor shedding during surgery is accomplished by the use of a specially designed non-slipping occlusive clamp on the vagina and by irrigating the vagina with 300 ml. of 3% formaldehyde solution. This is followed by flushing with saline. The vagina is then transected below the occlusive clamp and the specimen is removed.

1955 STOMACH CANCER FOLLOWING GASTRIC SURGERY FOR BENIGN CONDITIONS. (E.) Stalsberg, H. (Ullevål Hosp., Norway), and S. Taksdal. *Lancet* (7735):1175-1177, 1971.

An interval-dependent association between gastric cancer and previous surgery is studied in a necropsy series from Oslo. During the period 1960-1969, 17,070 adults were examined post mortem and in 630 cases gastric cancer was present. Each study case was matched by a control established through necropsy of a previously operated non-gastric cancer patient of the same age and sex. Detailed information for both groups was obtained from medical records acquired during clinical visits. Findings indicated that previous operations for gastric and duodenal ulcers occurred more frequently in gastric cancer patients than among the control group. The mean interval between an operation for a benign condition and death (excluding intervals of less than five years) was 26.4 years in test cases and 17.0 years in the control group. Longer post operation intervals showed sharply increasing over-representation of previous operations among gastric cancer patients. This trend was interpreted as being statistically significant when using the chi square test for trend. The advantages of using necropsy materials for analysing the association between gastric surgery and later development of cancer were: 1) accuracy attained in the type of procedure for ascertaining the presence of gastric cancer; 2) clinical observations made on the patient for a prolonged period post operatively. The gradually increasing gastric cancer risk of operated patients over increasing time spans seems to suggest a continuous carcinogenic influence rather than a single carcinogenic event during the patient's life. Findings indicate



that this increased risk is directly related to the establishment of a gastrojejunostomy with resulting gastritis and influx of bile, intestinal, and pancreatic fluids into the stomach.

1956 *Ampullarius australis* d'ORBIGNY (MOLUSCA, GASTROPODA) AS EXPERIMENTAL ANIMAL IN ONCOLOGICAL RESEARCH. A CONTRIBUTION TO THE STUDY OF CANCEROGENESIS IN INVERTEBRATES. (E.) Krieg, K. (Inst. Comparative Path., German Acad. Sci., Berlin) *Neoplasma* 19(1):41-49, 1972.

The significance of invertebrates in oncologic research is discussed. Results of investigations so far available indicate that neoplastic growth is exhibited by the so-called "half-stabil" animal species which possesses a limited regenerative capacity. *Ampullarius australis* d'Orbigny, a southern snail species, proved suitable for study. Over a series of eleven experiments 850 snails were injected with a 1% oily solution of 20-methylcholanthrene in a dose of 0.1 ml. Following a latency period of 95-150 days neoplastic processes were observed in three percent of the test organisms. Histological examination of these chemically induced tumor tissues showed them to be benign blastomas of epithelial origin. A metastatic process was seen in only one case. Transplantation experiments were carried out on a separate group of 168 snails. A malignant adenopapilloma was passaged successfully through three of the test gastropods. The rate of successful tumor transplant incidence in single passages was 69, 16 and 7%. In the transplant group, it was found that prolonged latent periods of the epithelial tumors of both the induced and transplant category seem to make the gastropods an especially suitable species for further carcinogenic investigation. Invertebrates, by their wide variety of species, phylogenetic position, and readily comprehensible structure present themselves as suitable vehicles for certain types of experimentation. The advantages of using gastropods are discussed in light of their ready availability, ease of maintenance in a laboratory situation and rapid supplementary breeding patterns.

1957 CODING PROPERTIES OF tRNA<sup>glu</sup> OF MAMMALIAN ORIGIN: COMPARISON BETWEEN RAT LIVER AND MINIMAL DEVIATION HEPATOMA 5123C tRNA's<sup>glu</sup>. (E.) Gonano, F. (Inst. Gen. Path., U. Modena, Italy) and G. Pirro. *Biochem Biophys Res Commun* 45(4): 984-990, 1971.

Isotopically labelled glutamyl-tRNA(tRNA<sup>glu</sup>) was prepared from crude tRNA isolated from normal rat liver and from Morris 5123C rat hepatoma and purified by chromatography on RPC-11 columns; and in accordance with results obtained by other authors multiple forms of tRNA<sup>glu</sup> were obtained. A minor peak (tRNA<sub>2</sub><sup>glu</sup>) was isolated from both normal liver and hepatoma, and was bound to the trinucleotide GAA, but not to the trinucleotide GAG. tRNA<sub>1</sub><sup>glu</sup> and tRNA<sub>3</sub><sup>glu</sup> was bound to both GAA and GAG. Although both were present in normal liver, tRNA<sub>3</sub><sup>glu</sup> was

absent from hepatoma cells. tRNA<sub>2</sub><sup>glu</sup> was presumed to be the same species isolated by Kimura-Hirada et al. which contained 5-methyl-2-thiouridine. Interpretation of these results in light of previous findings suggests that the ability of tRNA<sub>2</sub><sup>glu</sup> to bind only GAA is due to the presence of thiouridine in the first position of the anticodon.

1958 A NEW SYNTHETIC RNA-DEPENDENT DNA POLYMERASE FROM HUMAN TISSUE CULTURE CELLS. (E.) Fridlender, B. (Roche Inst. Molec. Biol., Nutley, N.J.), M. Fry, A. Bolden and A. Weissbach. *Proc Nat Acad Sci USA* 69(2):452-455, 1972.

Two DNA polymerases that can copy synthetic RNA polymers were isolated from cell homogenates of HeLa s-3 cells. The authors have previously found the same enzymes in WI-38 cells, but they have not been fully characterized. The enzymes were purified about 500-fold from the cell homogenates by DEAE-cellulose column chromatography followed by phosphocellulose column chromatography. The resulting two peaks showing polymerase activity were termed R-DNA polymerase I (the main peak eluting from phosphocellulose at 0.02 M KPO<sub>4</sub>) and R-DNA polymerase II (the minor peak eluting at 0.15 M KPO<sub>4</sub>). The purified synthetic R-DNA polymerase activity could be distinguished from similarly purified DNA-dependent DNA polymerases of HeLa cells by the following criteria: (1) The R-DNA polymerases could efficiently copy the ribo strand of the synthetic oligonucleotide-homopolymer complexes, (dT)<sub>12</sub>·poly(rA), poly(dT)·poly(rA) and (rU)<sub>29</sub>·poly(rA), to polymerize thymidylic acid, whereas the DNA-dependent polymerases were unable to use these primer templates. When the poly(rA) strand of (dT)<sub>12</sub>·poly(rA) is replaced with poly(dA), the R-DNA polymerases become almost inactive, whereas the nuclear DNA-dependent DNA polymerase I shows good utilization of the template. The R-DNA polymerases were able to copy a polyribo strand only in the presence of an oligoribonucleotide or oligodeoxyribonucleotide primer molecule. The primer molecule presumably formed a duplex structure with the template strand and supplied a 3'OH terminus for a chain elongation as previously reported necessary for the reading of RNA by the RNA-dependent DNA polymerases of the RNA tumor-viruses. (2) The R-DNA polymerases eluted from DEAE\* cellulose at 0.1 M KPO<sub>4</sub>, a concentration at which the known DNA-dependent polymerases are not found. (3) The conditions for optimal activity (Mn<sup>++</sup>, KCl, 30°C) for HeLa R-DNA polymerases were clearly different from those for HeLa D-DNA polymerases (Mg<sup>++</sup>, no salt, 37°C).

1959 ESTROGEN RECEPTORS IN HUMAN BREAST CANCER: 2. IN VITRO BINDING OF ESTRADIOL BY BENIGN AND MALIGNANT TUMORS. (E.) Hähnel, R. (Dept. Ob. Gyn., U. Western Australia, Subiaco), E. Twaddle and A. B. Vivian. *Steroids* 18(6):681-708, 1971.

A study of *in vitro* binding of estradiol by 108 breast tumors (37 benign, 71 malignant) was performed. The tumors were evaluated by *in vitro* reaction to tri-

tiated estradiol-17 $\beta$  using either soluble tissue homogenate fractions or tissue slices. In all cases the influence of competing unlabelled estradiol on the binding was determined. The data confirmed that there are two biochemically different types of human breast carcinomas, as determined by their estradiol affinity. Benign breast tumors bind little of the steroid compound. Breast carcinomas show two types of binding action: 1.) little binding of the steroid which is similar to the pattern in the benign tumors; and, 2.) the binding of considerably more estradiol with some evidence shown for the presence of specific receptors.

- 1960 STUDIES ON THE ABNORMAL HIGH BINDING CAPACITY OF BLOOD FOR VITAMIN B<sub>12</sub> IN CHRONIC MYELOID LEUKEMIA. (E.) Fischer, E. (Neurochem. Inst., Copenhagen, Denmark). *Clin Chim Acta* 36(2):409-418, 1972.

Experiments were designed to examine the binding of vitamin B<sub>12</sub> to the  $\alpha$ -globulin blood serum fraction in patients with chronic myeloid leukemia. Serum from 47 chronic myeloid leukemia patients was used. Assays of B<sub>12</sub> in these sera showed that serum B<sub>12</sub> values were increased in the leukemic patients; 91% of patients showed a serum vitamin B<sub>12</sub> level above 2000 pg/ml, with B<sub>12</sub> levels in normal serum samples averaging 455 pg/ml. No significant correlation was found between numbers of leucocytes in patients' samples and B<sub>12</sub> serum values. The B<sub>12</sub> binding capacity of serum was further investigated on leucocytes isolated from normal individuals and from chronic myeloid leukemia patients. The relative mobilities and relative percentage distribution of protein fractions separated by means of agar gel microelectrophoresis of concentrated leucocyte extracts from normals and chronic myeloid leukemia patients were examined. The leucocytes from leukemia patients revealed several more protein fractions in the electrophoretic mobility interval from 0.06-0.89 than occurred in normal leucocytes. This was the only distinct B<sub>12</sub> binding protein with an  $\alpha$ -globulin mobility shown by either normal leucocytes or patients' leucocytes. In immunoelectrophoretic analysis of leucocyte extracts (from normals and patients) incubated with <sup>58</sup>Co-labelled B<sub>12</sub>, only one B<sub>12</sub> binding protein was demonstrated. The finding that there is only one vitamin B<sub>12</sub> binding protein with  $\alpha$  mobility in normals as well as in chronic myeloid leukemia patients suggests that in chronic myeloid leukemia an increased number of leukemic leucocytes will liberate vitamin B<sub>12</sub> binding protein to the blood stream rather than liberating an abnormal leukemic protein with high serum B<sub>12</sub> binding capacity.

- 1961 SYRINGEAL HIDRADENOMA: AN UNUSUAL ECCRINE TUMOR. (E.) Shmunes, E. (U. Pennsylvania Sch. Med., Philadelphia), A. Izumi and H. Beerman. *Acta Dermatovenereol* 51(6):460-466, 1971.

A tumor of eccrine derivation was found on the

scalp of a 50-yr-old Caucasian male with a primary malignancy of the lung. The lesion was 8.5 by 5.5 cm, mildly pruritic, erythematous, flat and crusted. The patient had a history of trauma to the area of the tumor two years prior to hospitalization. Biopsy specimens indicated that the tumor was located in the dermis and was composed of tubules and islands of cells surrounded by a fibrous stroma. Many sweat glands, sebaceous glands, hair follicles and blood vessels were present. Based on histologic findings, the tumor was given the name "syringeal hidradenoma". Electron microscopy revealed ultrastructural features similar to those seen in immature intra-epidermal eccrine sweat ducts. The tumor differed from all other reported tumors of eccrine origin found in the literature.

- 1962 GANGLIOSIDES IN LEUKEMIC AND NON-LEUKEMIC HUMAN LEUKOCYTES. (E.) Hildebrand, J. (Intern. Med. Serv., Bordet Inst., Brussels, Belgium), P. A. Stryckmans and J. Vanhouche. *Biochim Biophys Acta* 260(2):272-278, 1972.

The level of lipid-bound sialic acid (gangliosides) of 18 purified leukocyte preparations was determined by silica gel G layer chromatography. Six of the preparations were from non-leukemic patients (group I) and were a mixture of polymorphonuclear cells (polys) (68-87%), lymphocytes (6-28%) and monocytes (2-9%). In group II (from six patients with chronic myelogenous leukemia), the preparations were composed of cells belonging to the myeloid series (94% or more, with 50% being polymorphonuclear in all but one case). In group III (from six patients with chronic lymphocytic leukemia) 93% or more of the cells in the preparations were small lymphocytes. The concentrations of lipid-bound sialic acid per gram of protein ranged from 164 to 308  $\mu$ g in group I and from 216 to 584  $\mu$ g in group II. Lymphocytes (group III) contained only trace amounts (10  $\mu$ g), and no gangliosides were found in lymphocytes obtained by catheterization of the thoracic duct of three uremic patients. In group II, there was no correlation between the level of gangliosides and the ratio of mature polys to immature forms of leukocytes from the myeloid series. Chromatographic analysis (using n-propanol-water as solvent) of gangliosides from groups I and II revealed two major spots, one migrating to about the same position as the Gm<sub>1</sub> brain ganglioside and the other migrating between Gm<sub>1</sub> and Gd<sub>1a</sub>. With chromatography of the same samples using a different solvent (chloroform-methanol-ammonia), the gangliosides were resolved in at least five components, with groups I and II showing different patterns. Chromatography of gangliosides extracted from patients with chronic lymphocytic leukemia (group III) revealed the presence of only one ganglioside which migrated as the authentic hematoside.

- 1963 D-GLUCOSE SUPPRESSION OF TYROSINE AMINO-TRANSFERASE IN RAT-HEPATOMA CELLS GROWN IN CULTURE. (E.) Mendelson, D. (New York U. Sch. Med., N.Y.), A. Grossman and A. Bocktor. *Europ J Biochem* 24(1):140-148, 1971.



Reuber H-35 rat hepatoma cells were grown in standard Dulbecco's medium. When the cells reached confluency, the standard medium was removed and replaced with Dulbecco's medium devoid of D-glucose but containing excess L-tyrosine. This modified medium induced a substantial increase in tyrosine aminotransferase activity. The response was biphasic; a slow enzyme increase was noted during the first 48 hr, followed by a rapid enzyme increase in the third 24 hr period. L-lysine and L-arginine, when substituted for L-tyrosine in the modified medium, produced the same result. No other L-amino acids nor D-tyrosine was effective in increasing tyrosine aminotransferase activity. The enzyme increase was due to net synthesis and not to reduction in the enzyme inactivation rate, since addition of inhibitors of protein synthesis (cycloheximide and actinomycin D) prevented transferase synthesis. Tyrosine aminotransferase induction in the absence of D-glucose was not due to lack of an energy source since 2-deoxyglucose, which is not metabolized beyond an initial phosphorylation, suppressed enzyme synthesis as effectively as D-glucose. A change in osmolarity brought about by the absence of D-glucose did not induce enzyme activity since replacement of D-glucose with an equivalent concentration of L-glucose did not prevent increased tyrosine aminotransferase synthesis. The data suggest that suppression of enzyme activity in this case is initiated at the cell membrane.

1964 INDUCTION OF TYROSINE AMINOTRANSFERASE WITH N<sup>6</sup>, O<sup>2</sup>-DIBUTYRL ADENOSINE 3'-5'-MONOPHOSPHATE IN RAT-HEPATOMA CELLS GROWN IN CULTURE. (E.) Grossman, A. (New York U. Sch. Med., N.Y.), A Boctor and Y. Masuda. *Europ J Biochem* 24(1):149-155, 1971.

Rat hepatoma cells were seeded in culture bottles containing either Dulbecco's medium alone or Dulbecco's medium with an excess of L-tyrosine. Two days later, the dibutyl analogue of adenosine 3':5' monophosphate (Bu<sub>2</sub>-Ado-3':5'-P) was added to both culture types. At various intervals thereafter, the cells were harvested and assayed for tyrosine aminotransferase activity. It was found that Bu<sub>2</sub>-Ado-3':5'-P stimulated enzyme activity only when the excess L-tyrosine was present, but did not alter cell permeability to tyrosine. In addition, the stimulation was found to be equivalent to that induced by the removal of glucose from the medium. No increase in tyrosine aminotransferase activity was noted, however, when the Bu<sub>2</sub>-Ado-3':5'-P was administered in the presence of either cycloheximide or actinomycin D. Further experimental variations also indicated that treatment with cortisol before, during, or after Bu<sub>2</sub>-Ado-3':5'-P did not potentiate enzyme activity; instead, these two substances acted independently of one another. It appears that the L-tyrosine sensitive-site is closely associated with the site of nucleoside cyclic monophosphate action (transcription).

1965 AN ACTIVITY FROM MAMMALIAN CELLS THAT UN-TWISTS SUPERHELICAL DNA: A POSSIBLE SWIVEL

FOR DNA REPLICATION. (E.) Champoux, J. J. (Salk Inst. Biological Studies, San Diego, Calif.) and R. Dulbecco. *Proc Nat Acad Sci* 69(1):143-146, 1972.

A partially purified nuclear extract from secondary mouse embryo cells was able to decrease the number of helix turns of closed-circular polyoma DNA in an *in vitro* assay system. The change in helix turns of the altered viral DNA was detected by a change in CsCl buoyant density banding secondary to increased binding of the dye, propidium diiodide. Enzyme activity of the extract was due neither to spurious binding of nuclear protein to viral DNA nor to nicking plus closure of viral DNA by polynucleotide ligase. Determination of superhelix density changes of viral DNA-ethidium bromide complexes treated with nuclear extract indicated that the extract enzyme definitely increased the number of negative turns of the polyoma DNA. It was concluded that the enzyme differed from a protein previously isolated from *E. coli*. The untwisting activity apparently required no cofactors. It was postulated that the mechanism of action might involve an enzyme-phosphate-polynucleotide intermediate which would allow the nicked strand to rotate relative to the helix axis. It is suggested that this activity might serve as a swivel during DNA replication.

1966 SERUM LYSOZYME AND VITAMIN B<sub>12</sub> BINDING CAPACITY IN MYELOPROLIFERATIVE DISORDERS. (E.) Catovsky, D. (Royal Postgrad. Med. Sch., London, England), D. A. G. Galton, C. Griffin, A. V. Hoffbrand and L. Szur. *Brit J Haemat* 21(6):661-672, 1971.

A study of 122 patients with various myeloproliferative disorders was undertaken to determine serum lysozyme (muramidase) and vitamin B<sub>12</sub> (TB<sub>12</sub>BC) binding capacity. Serum lysozyme levels were raised in monocytic leukemia and to a lesser degree in chronic granulocytic leukemia. Serum lysozyme levels increased in patients with hypercellular bone marrows and decreased in patients with aplastic or hypocellular marrows. One outstanding finding was a high serum lysozyme level in myelosclerosis. Serum folate levels were low when patients had high lysozyme concentrations. Results of the TB<sub>12</sub>BC studies showed an increase in myeloproliferative disorders, particularly in chronic granulocytic leukemia, in myelosclerosis and least in polycythemia rubra vera. It is concluded that TB<sub>12</sub>BC correlated with the total blood granulocyte pool, while serum lysozyme concentrations reflected granulocyte turnover.

1967 ENDOMETRIOID CARCINOMA OF THE OVARY. (Heb.) Czernobilsky, B. (Kaplan Hosp., Rehovot, Israel), N. Mass and M. Lancet. *J Israel Med Ass* 81(9):419-423, 1971.

A review of 47 primary ovarian adenocarcinomas treated from 1959-1970 in Israel yielded 12 (25.5%) endometrioid carcinomas. The clinical and pathological features of these neoplasms were compared with those of a similar study at the University of Pennsylvania. Incidence and clinical features were similar in both series although only 16.6% of the Israeli patients, as

compared with 41.3% of the American, were in clinical Stage I. Furthermore, while more than half of the American cases were classified as well differentiated, the majority of the Israeli cases showed poor histologic differentiation. The overall five-year survival rate of the Israeli patients was less than that of their American counterparts (30% versus 41%), although treatment in both series was similar and consisted of total hysterectomy followed by irradiation and chemotherapy. This difference was more striking when survival figures were analyzed according to clinical stages. Israeli patients in Stage I had 60% five-year survival as compared to 93% for the American patients in the same stage.

1968 LOSS OF THE CHOLESTEROL FEEDBACK SYSTEM IN THE INTACT HEPATOMA-BEARING RAT. (E.)

Bricker, L. A. (U. Texas Southwestern Med. Sch. Dallas), H. P. Morris and M. D. Siperstein. *J Clin Invest* 51(2):206-215, 1972.

The blunting of normal cholesterol feedback response in tumor-bearing rats as a potential means of detecting hepatomas in the intact animal is reported. The tumors employed were a highly differentiated hepatoma 7787, the well differentiated 9121 hepatoma, and the poorly differentiated 3924A hepatoma. Buffalo rats were implanted s.c. with 7787 tumor tissue; ACI/f Mai strain rats received hepatomas 9121 and 3924A intramuscularly. All transplanted rats were subsequently cholesterol-fed and triparanol-treated. Control animals which were triparanol-treated were separately maintained. Test animals were exsanguinated and plasma analyses by gas-liquid chromatography were completed. Data indicated that: 1) an accumulation of blood desmosterol was found in animals bearing hepatoma 7787, despite cholesterol feedback suppression; 2) a like desmosterol accumulation in hepatoma 9121-bearing animals reached levels of 93 mg/ml; and, 3) there were lower but significant concentrations of desmosterol in the blood of animals bearing the 3924A tumor. Evidence indicating that the tumor is a source of desmosterol is presented. Studies made on tissue slices for sterol content demonstrated that the tumor produces cholesterol through a desmosterol intermediate and that triparanol produces an almost complete suppression of desmosterol conversion to cholesterol in tumors. As a result, in hepatomas which normally produce significant amounts of cholesterol, desmosterol rather than cholesterol becomes the major end product of sterol synthesis. Confirmation was made of hepatoma-induced *in vivo* loss of cholesterol feedback by parenterally administering acetate  $^{14}\text{C}$  to the test animals. Isotopic analysis showed significant amounts of labeled cholesterol and desmosterol in the blood of triparanol-treated animals as contrasted to tumor-bearing animals, where large amounts of sterol- $^{14}\text{C}$  were recovered from the tumor itself.

1969 AN ELECTRON MICROSCOPIC STUDY OF THE BONE MARROW OF THE RAT IN AN EXPERIMENTAL MYELOGENOUS LEUKEMIA. (E.) Chen, L.-T. (Johns Hopkins U., Sch. Med., Baltimore, Md.), E. E.

Handler, E. S. Handler and L. Weiss. *Blood* 39(1): 99-112, 1972.

Alterations in the vascular sinus and hematopoietic compartment of rat bone marrow were observed with electron microscopy during the pathogenesis of an acute myelogenous leukemia. Thirty male rats weighing 180-200 g were injected i.v. with  $1 \times 10^7$  chloro-leukemic cells. Twenty of the animals survived and are the basis of this study. Three to four animals were sacrificed daily 7-12 days following the inoculation. As the disease progresses, the sinus wall becomes damaged and disintegrates; normal hemic elements disappear and the marrow compartment becomes packed with leukemic myeloblasts. Virus-like particles are present in the intercellular spaces and appear to bud from leukemic cells. The findings suggest a viral etiology for this leukemia.

1970 EXPERIMENTAL STUDIES ON THE CIRCULATORY DYNAMICS OF INTRAHEPATIC TUMOR BLOOD SUPPLY. (E.) Ackerman, N. B. (Menorah Med. Ctr., Kansas City, Mo.). *Cancer* 29(2):435-439, 1972.

Hepatic artery and portal vein perfusions of the normal liver and of solitary intrahepatic Walker tumor implants were studied in rats. Distribution of the capillary and precapillary circulation was measured using RISA and resin microspheres tagged with yttrium-90, resp. Results indicated that the tumors, when small, are nourished by both hepatic artery and portal vein blood. As the tumors grow larger, the arterial system becomes predominant, although portal vessels appear to terminate near the edges of the tumors. When blood flow through the portal system is acutely interrupted, the immediate reaction is that of a decreased relative perfusion of the tumors via the arterial system. A probable shunting of blood through the arterioles to the liver occurs. When blood flow through the hepatic artery is acutely interrupted, there appears to be little change in the distribution of portal blood to the tumor or liver. However, in about half of the rats studied by microcirculatory techniques, filling of the tumor plexus via the portal system was observed. When vasoactive drugs, both constrictors and dilators, were administered arterially, a decreased arterial perfusion of the tumors occurred. This change appeared to involve only the small arterial vessels.

1971 ALTERATIONS IN THE TRANSFER RNA POPULATION OF HEPATOMA 9618A AS COMPARED WITH NORMAL RAT LIVER. (E.) Volkers, S. A. S. (Microbiol. Dept., Indiana U., Bloomington) and M. W. Taylor. *Biochim Biophys Acta* 254(3):415-418, 1971.

The transfer RNAs (tRNAs) obtained from three rat hepatomas of varying degrees of differentiation were compared with the tRNAs obtained from normal rat liver. It was found that in the very poorly differentiated tumor (3924A) no differences occurred in the aminoacyl-tRNA; in the moderately well differentiated tumor (5213D) no differences were observed in Leu-, Lys-, and Tyr-tRNA, while in highly differ-



entiated tumor (9618A) differences were observed only in the Lys- and the Phe-tRNAs. However, alterations in the elution profiles did occur. Hepatoma 9618A, when compared to normal rat liver tRNA, exhibited two more Lys-RNA species of higher ionic strength and one more Phe-tRNA species. The molecular basis of these alterations is as yet unclear, but further studies are now being conducted.

- 1972 ANALYSIS OF THE CELL KINETICS OF HUMAN SOLID TUMORS. (E.) Terz, J. J. (Med. Coll. Virginia, Richmond), H. P. Curutchet and W. Lawrence, Jr. *Cancer* 28(5):1100-1110, 1971.

The cell cycle (tc) characteristics of seven human solid tumors (lung, maxillary antrum, malignant schwannoma, malignant melanoma, colon cancer, and two breast cancers) are described. Tumors were studied by pulse labelling with intravenous tritiated thymidine and multiple biopsies. Observations of the standard components of the cell cycle were made by radioautography and by the percent of labelled mitosis curve, the grain halving method, and computer model (G. G. Steel) which allows the determination of the variants of each component of the cycle. The results showed the tc ranged from 14 hrs. (lung cancer) to 44 hrs. (schwannoma) with the DNA synthetic period ranging from 5.5 hrs. (lung cancer) to 21 hrs. (melanoma). A major discrepancy was found between the calculated tumor doubling time and the measured doubling time. The rate of cell loss was 11% (lung cancer) to 86% (melanoma). The growth fraction was 25% (breast cancer) and 80% (lung cancer). The use of different methods apparently did not affect the estimation of the cell cycle. When frequent samples were obtained a second wave of labelled mitoses was always shown. Wide variation in the duration of the cell cycle in different tumors was noted but, to date, no definite correlation can be established between the type of tumor and the kinetics of the cell components.

- 1973 CHROMOSOMAL ANALYSIS OF LYMPHOBLASTOID CELL LINES FROM PATIENTS WITH LEUKAEMIA, INFECTIOUS MONONUCLEOSIS, OR BURKITT LYMPHOMA. (E.) Macek, M. (Baylor Coll. Med., Houston, Texas) and M. Benyesh-Melnick. *Neoplasia* 19(1):51-56, 1972.

Chromosomal analyses were carried out on Epstein-Barr (EB) virus-positive and EB virus-negative lymphoblastoid cell lines derived from three patients with acute lymphoblastic leukemia (L48, L56, L77) and seven patients with infectious mononucleosis (IM29, IM58, IM82, IM529, IM566, IM935, IM964) and were compared to analyses of EB2, EB3 and P3J Burkitt lymphoma cells and of two cell lines (AMC30, NC37) derived from normal individuals. Most of the lines were examined at different passages during a 61-month cultivation period. At the time the cells were harvested for chromosomal analysis, they were examined by immunofluorescence and electron microscopy for the presence of EB virus. EB virus was

detected in all three Burkitt lymphoma lines, one of the three lines from patients with acute leukemia, and five of the seven lines from patients with infectious mononucleosis. Neither of the two normal lines was positive for EB virus. Results of chromosome analysis indicated that no significant anomalies in chromosome number could be associated with the presence of EB virus. A diploid number of chromosomes was maintained throughout the 61-month period in lines EB2, EB3, L48, L77 and AMC30. A shift of chromosome number to hyperploidy with 47 or 48 chromosomes was seen in lines P3J, L56, IM39, IM529 and NC37, with the shift in at least the IM39 line being time-dependent. Only infectious mononucleosis lines (IM58, IM529, IM566) revealed a complete shift to heteroploidy after a long time in culture. The common types of marker chromosomes ( $m_2$ ,  $m_B$  and  $m_T$ ) were detected in all the 15 lines examined, regardless of origin of derivation or presence of EB virus. Cells with these chromosomal aberrations appeared to have selective advantage of growth *in vitro*, as a passage level-dependent increase in frequency of clones with markers  $m_2$ ,  $m_B$  and  $m_T$  was observed. Trisomy C was the most frequent type of chromosomal rearrangement in all groups studied (seen in EB2, P3J, L56, IM39, IM529, NC37, EB3, IM935 and IM964). Cell clones with trisomy G were seen in lines EB2 and IM58. A passage level-dependent increase in frequency of clones with trisomy C and G was also observed. The results of the study also indicated that Cqh+ marker, suspected as a possible indicator of EB virus infection, could be found with equal low frequency (0-9%) in both EB virus-positive and EB virus-negative cell lines.

- 1974 CHARACTERISTICS OF THE POLYADENYLIC ACID SEGMENT ASSOCIATED WITH MESSENGER RIBONUCLEIC ACID IN MOUSE SARCOMA 180 ASCITES CELLS. (E.) Mendecki, J. (Tufts U. Sch. Med., Boston, Mass.), S. Y. Lee and G. Brawerman. *Biochemistry* 11(5):792-798, 1972.

Polysomal (messenger) and nuclear RNA (nRNA) of mouse sarcoma 180 ascites cells prelabeled with either  $^3H$ -adenosine or  $^{32}P$  in the presence of 0.04  $\mu g/ml$  actinomycin D and 1  $\mu g/ml$  ethidium bromide were analyzed for polyadenylic acid (polyA) content. Cell nuclei were separated from the cytoplasmic fraction of cell lysates by centrifugation (1000 g, five min). Polysomal RNA (pRNA) was prepared either by phenol extraction in the presence of 0.1 M Tris (pH 9.0) or by sequential extractions at pH 7.6 and 9.0. Nuclear RNA was extracted with phenol and digested with DNase (5  $\mu g/ml$ ). Poly A segments were isolated from RNA preparations by pancreatic RNase treatment (1  $\mu g/ml$ ) followed by slow filtration through Millipore filters. The filters were either dried and counted for radioactivity or the poly A was recovered and analyzed for nucleotide composition by paper chromatography or subjected to polyacrylamide gel electrophoresis. The extent of adenosine label in poly A of pRNA was 30 to 70% of total radioactivity. Although a smaller proportion of poly A was detected in nRNA than in pRNA, the total amount of radioactive poly A in the nuclear extracts was almost equal to that of the polysomes. The polyA-containing pRNA consisted

of a heterogeneous population of molecules (10-30S) and showed a DNA-like base composition (21-26% A, 23-29% G, 22-27% C, 23-28% U). Nucleotide analysis of the isolated nuclear and polysomal poly A showed an adenylate content of 97-99 mole percent. About 0.5 mole percent adenosine was seen in alkyllyne hydrolysates of this material, suggesting an average chain length of 200 nucleotides for the poly A segment, as well as the presence of a free 3'-OH terminus. The time course of poly A labeling in polysomes indicated that this sequence was assembled after the rest of the RNA molecule had been completed. The rate of labeling of nuclear poly A was greater than that of polysome poly A. Poly A synthesis was strongly inhibited by actinomycin D (10 µg/ml), but the effect was smaller than that on total RNA. These results tended to rule out separate poly A synthesis followed by joining to completed RNA chains. Cordycepin (25 µg/ml) preferentially inhibited poly A synthesis resulting in shortened poly A segments as evidenced by increased mobility in polyacrylamide gels. The fact that <sup>3</sup>H-adenosine was incorporated into poly A of cordycepin-treated cells indicated that the drug functioned by inhibiting an enzyme concerned with poly A synthesis without becoming incorporated in the polymer. Polyacrylamide gel analysis also indicated that in untreated cells the polysomal poly A was shorter than the nuclear material.

- 1975 OBSERVATIONS ON CELL PROLIFERATION IN HUMAN MYELOCYTES. (E.) Wickramasinghe, S. N. (St. Mary's Hosp. Med. Sch., U. London, England) and B. Moffatt. *Acta Haemat* 46(4):193-200, 1971.

The relationship between size of myelocytes and their position in interphase was investigated, and the extent to which the promyelocyte-myelocyte pool is altered in disease was reviewed. Bone marrow aspirates were obtained from both normal and hematologically diseased patients. These aspirates were either studied under standard May-Grunwald-Giemsa stain, or were subjected to Feulgen microspectrophotometric techniques to measure the degree of DNA replication in individual nuclei. The myelocyte increased in size as it passed through the replication interphase; the old classification of large myelocyte is known to include the majority of late S and G<sub>2</sub> phase cells. It was also found that the indices of promyelocytes and myelocytes in patients with reactive neutrophil leucocytosis were 15% higher than that of normal patients, indicating a significant increase in cell proliferation. Such high values were not encountered in other blood diseases studied. It is therefore likely that the high myelocyte labelling indices result from a prolongation of DNA synthesis rather than from a shortening of interphase.

- 1976 COMPARATIVE CHARACTERIZATION OF THE PHYSIO-CHEMICAL PROPERTIES OF DNA OF NORMAL AND MALIGNANT MOUSE FIBROBLASTS IN TISSUE CULTURE. (E.) Kuz'mina, S. V. (U.S.S.R. Acad. Sci., Pushchino) and N. B. Strazhevskaya. *Biophysics* 15(6):1178-1181, 1970.

It has been postulated that: 1) there are differences between the quantitative content of DNA in tumor and normal tissue; and 2) there are variations in the nucleotide composition and sequence of DNA in tumor and normal cells. To test both of these possibilities, fibroblasts were derived from mouse embryo tissue of the subline C<sub>3</sub>HfpuII. These cells exhibit normal characteristics in the early passages, but after a length of time *in vitro* transform spontaneously into malignant cells capable of producing tumors *in vivo*. Therefore, by use of these fibroblasts, it was possible to experiment concurrently on both normal and transformed cells derived from the same subline. Experimentation consisted primarily of DNA isolation according to the method of Georgiyev-Struchov. In addition, both the viscosity and elastoviscosity of the DNA preparation was higher for normal than for transformed cells. From results obtained, it is concluded that the proteins of DNA in normal and in transformed fibroblasts do differ. It is suggested that the malignant fibroblasts lose two isoenzymes of lactate dehydrogenase, probably because the site of synthesis is blocked by protein. This protein converts portions of the DNA from euchromatin to heterochromatin, resulting in a stronger, less easily broken DNA complex.

- 1977 STEROID BIOSYNTHESIS *IN VITRO* BY TRANSPLANTABLE INTERSTITIAL CELL TUMOR OF MICE: III. METABOLISM OF PREGNENOLONE IN THE CULTURED TUMOR CELL. (E.) Inano, H. (Nat'l. Inst. Radiol. Sci., Chiba, Japan), B. Tamaoki and Y. Tsubara. *Endocrinology* 90(1):307-310, 1972.

A primary culture of a testicular interstitial cell tumor derived from the KF mouse strain was exposed to carbon-14-labelled pregnenolone. After an incubation period, the cells were harvested and the steroids were extracted. Quantitation of the radioactivities of the metabolites indicated that pregnenolone was converted to progesterone, and 3α-hydroxy-5α-pregnan-20-one and to other androgens and testosterone, but not to corticoids. On the other hand, when pregnenolone was incubated with slices of cell tumor tissue from the testes, the metabolites 11-dexycorticosterone and 11β- and 18-hydroxylated corticoids were detected. That no 21-hydroxylated metabolites were detected in cell culture suggests that the *in vitro* cultured cells seem to lose the 21-hydroxylase activity or to retain it in an inactive form. However, enhancement of Δ<sup>4</sup>-5α-hydrogenase and 3α-hydroxysteroid dehydrogenase activities was noted. A possible metabolic pathway for steroid biconversion is presented.

- 1978 ADRENAL FUNCTION IN CANCER: RELATION TO THE EVOLUTION. (E.) Saez, S. (Berard Ctr., Lyon, France). *Europ J Cancer* 7(5):381-387, 1971.

The rate of cortisol production and 17-hydroxy corticosteroid (OHCS) excretion was studied in 21 men and 12 women bearing different types of tumors with miscellaneous histological patterns, and in 31 women with mammary carcinoma. Determination of cortisol production by isotope dilution and OHCS excretion level



was completed following a series of three tests carried out on each patient in the following manner: 1) under basal conditions; 2) on the third day of administration of dexamethasone (DM) at a 20 µg/kg/day dose; and 3) on the third day of administration of DM at an 8 mg/day dose rate. In all patients there were elevated cortisol and OHCS urinary excretion levels in the basal state. Treatment with DM 20 µg/kg/day reduced both levels, although they were still increased as compared to normal levels. The administration of DM 8 mg/day reduced cortisol production and OHCS excretion by 50% in those patients unresponsive to the low DM dose. Study of 31 cases of breast cancer failed to indicate a definite correlation between cortisol and OHCS levels and the stage of disease as classified by Taylor. A highly significant correlation was found when patients were classified according to whether or not they had experienced recurrences or had improved within the previous six months. Response to DM treatment was better and cortisol production and OHCS excretion were lower in the nonrecurrent and improved groups.

1979 BILHARZIAL CARCINOMA OF THE BLADDER WITH PREGNANCY AND LABOR. (E.) Badawy, S. (Ain Shams U., Cairo) and M. Karim. *Int Surg* 56(6):434-437, 1971.

A study of 11 cases of bilharzial carcinoma of the bladder in pregnant Egyptian women is reported. The average age of the women at diagnosis was 32.8 years. The microscopic study of these tumors showed squamous cell carcinoma, indicating a previous metaplasia. It was thought that local irritation, disintegrated bilharziasis worms and ova, and the tissues destroyed as a result of their deposition, lead to the production of tryptophane. Tryptophane was thought to be acted on by some urinary enzymes, resulting in the release of carcinogenic orthophenols. A marked rise in β-glucuronidase in the urine of bilharzial bladder carcinoma patients was found.

1980 STUDIES ON THE INDUCTION OF DNA POLYMERASE DURING TRANSFORMATION OF HUMAN LYMPHOCYTES. (E.) Agarwal, S. S. (Inst. Cancer Res., Philadelphia, Pa.) and L. A. Loeb. *Cancer Res* 32(1):107-113, 1972.

The effects of inhibition of RNA synthesis by actinomycin D (ACD, 0.02 or 0.4 µg per ml) and inhibition of protein synthesis by puromycin (10 µg per ml) on the increase in DNA polymerase activity and the incorporation of <sup>3</sup>H-thymidine into human peripheral lymphocytes transformed by phytohemagglutinin (PHA) is studied. PHA-stimulated lymphocytes normally begin to incorporate <sup>3</sup>H-thymidine after 15 hr. DNA polymerase activity normally begins to increase two to three hr before this. Neither ACD (0.02 µg per ml) nor puromycin had any effect on basal polymerase activity of nonstimulated lymphocytes, suggesting little turnover of the enzyme under these conditions. When ACD (0.02 µg per ml) was added two hr after the addition of PHA, no increase in DNA

polymerase activity was seen. Polymerase activity of stimulated lymphocytes was able to increase to 50% of maximum stimulated value when ACD was added six hr after PHA. The inhibition of polymerase by ACD was nearly paralleled by a decrease of thymidine incorporation into acid insoluble material. Addition of ACD at 16, 20 and 24 hr after PHA had very little effect on the increase in polymerase activity even though uridine incorporation into RNA was inhibited by 73, 72.8 and 74% resp. The insensitivity of the lymphocytes at these later time periods was not due to depletion of ACD. Differences in sensitivity were not due to changes in the permeability of lymphocytes to ACD, as the rate of uptake of radioactive ACD actually increased with time. Induction of DNA polymerase activity thus appeared to be programmed by an ACD sensitive RNA product made between two and six hr after addition of PHA. The continued increase in polymerase activity did not require continued synthesis of RNA, as complete inhibition of RNA synthesis by ACD produced no decrease in polymerase activity at later times. Continued synthesis of polymerase was required to maintain a particular level of activity in PHA-stimulated lymphocytes since inhibition of protein synthesis by puromycin resulted in exponential degradation of existing activity. That polymerase was not synthesized in an inactive form during the first 20 hr after PHA stimulation was shown by the inability of homogenates from long term (>20 hr) stimulated cultures to activate lymphocytes exposed to PHA for less than 20 hr. It is suggested that the RNA template for polymerase activity is made early and translated into active enzyme at a later time.

1981 THE METASTATIC BEHAVIOR OF A SPLEEN-TROPIC RETICULUM CELL SARCOMA IN SPLENECTOMIZED MICE. (E.) Pilgrim, H. I. (U. Utah Coll. Med., Salt Lake City). *Proc Soc Exp Biol Med* 138(1):178-180, 1971.

The metastatic behavior of a spleen-tropic reticulum cell sarcoma is studied. Two month-old C3Hf/Pi mice were grouped as follows: (1) 26 mock-operated mice (spleen visually examined but left intact) were designated as controls, (2) 25 mice were splenectomized. On the 25th post-operative day, each animal in both groups received a 0.05 ml injection of a tumor cell suspension (reticulum cell sarcoma, type B of Dunn) containing approximately 37,000 cells/mm<sup>3</sup>. The inoculations were made into the subcutaneous tissue of the animals' flank. Results showed that splenectomized animals survived longer than those with spleen intact. Autopsy on these animals showed consistent metastasis to liver, kidneys and lymph nodes. Mock-operated animals had massive spleens with an obviously immense amount of tumor present therein. Testing showed that onset of death in splenectomized animals was delayed; however, once it began, animals in both groups died at approximately the same rate. It is postulated that cells sequestered by the spleen are thus protected and therefore not destroyed. A rather high percentage of circulating cells in the splenectomized animals are destroyed.

- 1982 GROWTH HORMONE-SECRETING VARIANTS OF A MAMMOTROPIC TUMOR. (E.) Ito, A. (Dept. Path., Columbia U., New York, N.Y.), J. Furth and P. Moy. *Cancer Res* 32(1):48-56, 1972.

Radioimmunoassay (RIA) and immunohistochemical staining (IHS) techniques are used to characterize the somatic Hollander variant (MtT.W5/OM) of MtT.W5., a mammotropic pituitary tumor (MtT) isolated in 1961 from a Wistar-Furth rat which had been X-rayed over the head and neck. The variant was renamed W5/St.H by the authors according to conventional genetic terminology. W5/St.H was transplanted s.c. and the rate of growth was equal in male and female rats and was not affected by castration. The only morphological difference noted between W5/St.H and the original MtT.W5 was increased variability in size and shape of the W5/St.H cell with an increased number of mitoses. A marked increase in body weight and a proportional increase in weight of body organs indicated secretion of somatotrophic hormone (StH) by W5/St.H. Increases in weight were directly related to tumor size and age. Mammary gland hyperplasia was conspicuous at autopsy in rats with large tumors and a long tumor-bearing period. Milk secretion, a characteristic of the usual MtT strain, was slight or absent. Serum levels of both StH and Mth (mammotropic hormone) progressively increased with the tumor size in rats of both sexes. Mth levels were eight to 23 times normal and StH levels were 220 to 230 times normal as determined by RIA in male and female rats with tumors about five cm. in diameter. IHS studies were performed on sections from tumors and pituitaries of W5/St.H-bearing rats. The tumors stained well for StH but the intensities of the staining in different cells varied greatly. Staining for StH per cell in pituitaries of rats bearing tumors was generally more intense than that in tumors but was less intense than in pituitaries of controls. Staining of tumors with anti-Mth was weakly positive. Many cells remaining unstained. Mth-secreting pituitary cells of tumor-bearing hosts were fewer than those of controls. Mth, unlike StH, was concentrated in one "pole" of the mammotropic pituitary cells, forming a cap over the unstained nucleus. W5/St.H was able to support the growth of Mth-dependent tumors (MT9) grafted onto W5/St.H-bearing mice, thus indicating that W5/St.H could secrete both StH and Mth. The results support earlier findings of the intimate relation of Mth and StH production and are consistent with the hypothesis that the same neoplastic acidophils produced both hormones.

- 1983 PRODUCTION OF INTERFERON INDUCED BY HYALURONIC ACID FROM ROUS SARCOMA. (E.) Watanabe, M. (Osaka Prefectural Inst. Public Hlth., Japan) and M. Sato. *Cancer* 29(2):517-523, 1972.

An acid mucopolysaccharide, probably hyaluronic acid (HA), in the phenol extract of Rous sarcoma tumor tissue can induce production of an interferon (IF)-like inhibitor in chick embryo cell cultures. The nature of this IF-like inhibitor, and of the inducer of the IF-like activity, was studied.

Rous tumor tissue formed on chick chorioallantoic membrane (CAM) inoculated with Rous sarcoma virus (RSV) was used. HA from the tumor tissue was purified with cetyltrimethylammonium bromide (CTAB) prior to phenol extraction of tumor tissue. The growth rate of RSV in cultures of chick embryo cells treated with phenol extract from Rous tumor formed on CAM inoculated with RSV was reduced to 50% or less of that in untreated cell cultures. Alteration of cells by RSV was also inhibited; this inhibition was mediated by production of an inhibitor in the culture fluids of treated cells. The inhibitor was cell species-specific but not virus-specific; it had no effect on vesicular stomatitis virus (VSV) growth in L cell cultures, but did inhibit VSV growth in chick cell cultures. Actinomycin D blocked inhibitor production and also blocked the activity of inhibitor already produced. It was thought that this inhibitor was IF itself. The molecular weight of the IF produced was 68,000. The inducer of the IF inhibitor in Rous sarcoma phenol extracts was examined; the IF-inducer was purified by CTAB fractionation, and the nucleic acid-free HA fraction was obtained. This fraction had IF-inducing activity which was inactivated by hyaluronidase treatment. The IF-inducer was thought to be HA of a special nature different from the HA of human umbilical cord or normal CAM of chicken egg. The tumor HA had a linear dose-response for the IF-inducing capacity between 4.8 µg/ml and 10.0 µg/ml, and a plateau over this value.

- 1984 RNA-DEPENDENT DNA-POLYMERASE ACTIVITY IN HUMAN TUMORS. (E.) Reid, T. W. (Yale U. Sch. Med., New Haven, Conn.) and D. M. Albert. *Biochem Biophys Res Commun* 46(2):383-390, 1972.

Experiments performed to determine whether RNA-dependent DNA polymerase is present in certain human tumors and in normal tissue from sites corresponding to the tumor sites are described. Surgical or autopsy specimens were obtained of medulloblastoma, neuroblastoma, retinoblastoma and choroidal malignant melanoma, and of normal cerebellum, connective tissue and normal retina and choroid. Two different templates were used in assays for RNA-dependent DNA polymerase activity, poly(A)·oligo(dT) and poly(A)·poly(dT), with RNA-dependent DNA polymerase activity being found in medulloblastoma specimens on both templates. The enzyme was demonstrated in the cell homogenates and activity remained in the centrifuge supernatant fluid at 30,000 x g after 30 min and in pellets at 100,000 x g in two hr. When tissue homogenates of medulloblastoma were subjected to 30,000 x g centrifugation, about 88% of RNA-dependent DNA polymerase activity in supernatant and pellet fractions required detergent treatment in order to be evident. RNA-dependent DNA polymerase activity towards poly(A)·oligo(dT) was also found when homogenates of retinoblastoma, neuroblastoma and choroidal malignant melanoma were reacted with template and tritium labelled thymidine triphosphatase. However, en-



zyme activity was present in these tumors in lower amounts than was found with medulloblastoma. Corresponding normal tissues showed no RNA-dependent DNA polymerase activity. It is postulated that an actual viral reverse transcriptase, possibly related to a RNA-oncogenic virus or a new enzyme with characteristics differing from any known DNA polymerase, may have been present.

1985 JUNCTIONS BETWEEN CANCER CELLS IN CULTURE: ULTRASTRUCTURE AND PERMEABILITY. (E.)

Johnson, R. G. (Dept. Zool., U. Minnesota, Minneapolis) and J. D. Sheridan. *Science* 174(4010):717-719, 1971.

A study employing Novikoff hepatoma cells (N1S1-67) was conducted to characterize the junctions between cancer cells in culture. Electron microscopic, electrophysiologic and dye-injection techniques were used to study N1S1-67 cells growing in suspension cultures. It was found that true tight junctions (regions of fusion of apposed membranes) and desmosomes are either quite rare or totally absent, while gap and intermediate junctions are present. It was shown that small ions and certain dyes were readily exchanged through the gap junctions.

1986 ENDOPLASMIC RETICULUM, LIPID, AND GLYCOGEN OF MORRIS HEPATOMAS: COMPARISON WITH ALTERATIONS IN HEPATOCYTES. (E.) Hruban, Z. (Dept. Path., U. Chicago, Ill.), Y. Mochizuki, H. P. Morris and A. Slesers. *Lab Invest* 26(1):86-99, 1972.

Thirty-five hepatomas with different growth rates, several normal livers from Buffalo rats, and livers from tumor-bearing rats were obtained after exsanguination under light anesthesia and were observed under the electron microscope. Scanning X-ray elemental analysis was performed on selected specimens. Recognizable morphologic alterations and patterns were compared with reported changes produced in hepatocytes by physiologic and pathologic stimuli. Rough endoplasmic reticulum (RER) was altered in all hepatomas. Changes consisted of depletion of ergastoplasm, disorganization of cisternae, wrapping of cisternae around mitochondria, meandering cisternae, irregular distribution of ribosomes on cisternae, vesiculation of rough cisternae, dilation of cisternae, reticular "fingerprints" consisting of abundant tubular smooth reticulum and of peripheral flat smooth cisternae, and abundance of free ribosomes. Such changes were not, however, specific for the neoplastic process as they also occurred in physiologically and pathologically altered liver cells. Smooth vesicles within lumina of RER and smooth endoplasmic reticulum (SER) were found only in neoplastic cells. Fast growth rate was often, but not always, associated with a paucity of RER. Stacked rough cisternae were found only in a few hepatomas. The spacing of ribosomes of cisternae in Morris hepatoma cells was often irregular compared to the regular spacing seen in normal hepatocytes. Free ribosomes were abundant in the cytoplasm of Morris hepatomas. Short rough cisternae and rough

vesicles were also found in many hepatomas. Large electron dense inclusions were observed within rough cisternae of two hepatomas and were shown to contain calcium and to lack phosphate and fluoride. Whereas normal hepatocytes contained predominantly the tubular form of SER, Morris hepatoma cells contained tubular and vesicular SER in different amounts. Fast growing hepatomas contained either small amounts of SER or lacked it completely. Glycogen was found on electron microscopic examination of several hepatomas and was usually associated with tubular SER and with glycogen "fingerprints." Lipid-like material was present in ten of 35 hepatomas. Correlation of growth rates with the structure of endoplasmic reticulum (ER) showed that "fingerprints" were more commonly found in hepatomas with moderate growth rates. Fast growing hepatomas had a simplified ER. The smooth vesicles found in lumina of RER and SER of many hepatomas are thought to represent a characteristic lesion of the neoplastic ergastoplasm.

1987 EARLY MALIGNANT DISEASE OF THE CHORION. (E.) Teoh, E. S. (Dept. Ob. Gyn. U. Singapore), S. S. Ratnam and M. Y. Dawood. *Acta Obstet Gynec Scand* 50(3):247-252, 1971.

The clinical features, prognosis and management of choriocarcinoma occurring in 51 of 532 cases of hydatidiform mole present in a population of Singapore females are discussed. Although malignancies were present in all age groups, a significantly increased incidence was observed in patients over 40 years of age (14.6% compared to a general incidence of 9.6%). Among the 15- to 40-year age group, there appeared to be a slightly increased incidence between 35 and 39 years. Incidence of malignancy in women para 3 or greater was not significantly increased over women para 2 or below. Malay patients had a greater tendency to develop early malignant disease of the chorion (15.8%) than non-Malay patients (7.1%). Of the cases studied 21 showed no metastases. Of the 30 cases with metastases, the most common site was in the lungs (27 cases) although metastases to the vagina, vulva and brain were also observed. A rise in gonadotropin titer was characteristically seen in chorionic malignancy, the degree of increase being proportional to the amount of functional malignant tissue. Oral or parenteral treatment with methotrexate was used in conjunction with surgical excision. Women over 40 years or patients para 3 or greater were treated by hysterectomy in addition to chemotherapy. The necessity for early detection of choriocarcinoma, if treatment is to be successful, was emphasized.

1988 NECROSIS OF TUMOUR CELLS RELATED TO CIRCULATORY INSUFFICIENCY IN PULMONARY TUMOUR EMBOLISM. (E.) Svanes, K. (U. Bergen, Sch. Med., Norway). *Acta Path Microbiol Scand* 79:533-560, 1971.

A case history of a 74-yr-old woman with an epidermoid carcinoma of the cervix uteri is evaluated to determine whether necrosis of tumor cells in pulmonary tumor emboli was due to circulatory insufficiency.

Under the microscope, many small arteries, arterioles and capillaries were found to contain tumor cells. Vessels in 6% of 128 cross sections of arteries and arterioles were completely occluded by viable and dead tumor cells; 25% of vessels were occluded by tumor cells together with thrombus masses; 39% of vessels were occluded by tumor cells and connective tissue. Necrotic tumor cells were found farther away from the nutritive blood vessels than viable tumor cells. Tumor cells were found growing along the vessel wall and appeared viable, while intravascular tumor growth was poor in arteries with extensive perivascular tumor infiltration. The tumor grew well in perivascular lymphatic vessels. The data support the hypothesis that necrosis of tumor cells in pulmonary emboli is probably due to nutritional insufficiency caused by circulatory disturbances.

- 1989 PROTEIN CATABOLISM: ACTIVITIES OF THREE PROTEOLYTIC ENZYMES IN A SYNCHRONIZED L5178Y MOUSE LEUKEMIC CELL LINE. (E.) Bosmann, H. B. (Sch. Med. Dent., U. Rochester, N.Y.). *Int J Protein Res* 3(5):271-276, 1971.

Activities of proteolytic enzymes in a synchronized L5178Y mouse leukemic cell line were investigated. The following proteolytic activities (in  $\mu$ g pronase equivalents per hour per mg protein) were found; 1) general proteolytic (azocoll substrate) 120; 2) cathepsin 42; 3) trypsin 21. No detectable collagenase activity was noted. A double peak enzyme with peaks in the M and the mid-S phases of the cell cycle represented the general proteolytic activity, whereas cathepsin was distributed as a double peak enzyme with a narrow peak in mid-S and high activity in M. A pattern described as either a double peak enzyme or a continuous enzyme with depressions of activity at early S and G<sub>2</sub> was demonstrated for trypsin. It should be noted that in these experiments enzyme activity and not enzyme synthesis or degradation is measured. It was thought that local environmental factors *in vivo* may be controlling the activities of the enzymes studied.

- 1990 EFFECTS OF BACILLUS CALMETTE-GUERIN (BCG) INFECTION ON RESIDUAL DISEASE OF THE RAT MAMMARY TUMOR AFTER OVARIECTOMY. (E.) Piessens, W. F. (Tumor Ctr., U. Brussels, Belgium), R. Heimann, N. Legros and J.-C. Heuson. *Europ J Cancer* 7(5):377-380, 1971.

Virgin, random-bred Sprague-Dawley female rats having 7,12-dimethylbenz(a)anthracene-induced mammary tumors were treated with Bacillus Calmette-Guérin (BCG), a nonspecific stimulator of the reticulo-endothelial systems, after the animals had undergone ovariectomy. Normally, tumors would begin to regress after ovariectomy and would reach a maximum state of regression three weeks later. Following this, the tumors would resume growth. This pattern occurred both in control rats and in rats given BCG prior to ovariectomy. Weekly s.c. injection of BCG beginning three weeks after ovariectomy arrested further tumor

growth. Administration of a single BCG dose three weeks after ovariectomy arrested growth for an additional three weeks, after which growth resumed.

- 1991 PROTEINS ASSOCIATED WITH GLOBIN MESSENGER RNA IN AVIAN ERYTHROBLASTS: ISOLATION AND COMPARISON WITH THE PROTEINS BOUND TO NUCLEAR MESSENGER-LIKE RNA. (E.) Morel, C. (Swiss Inst. Exp. Res. Cancer, Lausanne), B. Kayibanda and K. Scherrer. *FEBS Letters* 18(1):84-88, 1971.

A study of messenger RNA-protein (mRNP) complexes is presented in a highly differentiated system--duck immature red blood cells. Polyribosomal mRNP was purified and nuclear messenger-like RNA-protein (mRNP) isolated; the protein samples were then subjected to gel electrophoresis. The purified mRNP was found to have an S value of about 20 and was free of ribosomal or hemoglobin contamination. The polyribosomal globin-mRNA prepared by EDTA dissociation is associated with two predominant proteins of 73,000 and 49,000 molecular weight. Results of electrophoresis indicate that the nuclear protein moved faster than the mRNP protein bands. It appears that similar mRNA's are associated with different proteins in different species and are very specific to a given mRNA, whereas proteins associated with nuclear mRNA seem to be identical in all cells.

- 1992 MAST-CELL NEOPLASMS OF THE DOMESTIC CAT. (E.) Garner, F. M. (Armed Forces Inst. Path., Washington, D. C.) and C. H. Lingeman. *Path Vet* 7(6):517-530, 1970.

Histologic material from 16 cats with mast cell tumor was compared with previously reported mast cell tumor features of cats, dogs and man. Ten of the 16 tumors were cutaneous, four were in hematopoietic tissue and two were found in the intestinal wall. Histologic features were similar to those of dog mast cell tumors. Skin tumors were fairly well-localized and of varying degrees of differentiation, and were found in the dermis or subcutaneous tissue and adnexal structures. Mature blood eosinophils were seen in only two of ten primary skin tumors. With Giemsa stain, cytoplasmic granules of varying numbers of cells stained magenta, purple or blue; the numbers and sizes of stainable granules varied greatly in different cells of the same tumor or in different tumors. Primary cutaneous tumors of five cats stained with PAS had red granules in at least 90% of cells. Only one cat with a primary tumor of the skin was known to develop a subsequent abdominal tumor. Visceral tumors tended to be less well-differentiated than skin tumors and some could easily be confused with lymphoma, plasma cell tumor or granulocytic sarcoma. Four of the six primary visceral mast cell tumors mainly involved hematopoietic viscera while two were apparently primary in intestinal walls. Visceral tumors were not seen to metastasize to skin.



- 1993 INDUCTION OF HYPERPLASIA IN MOUSE SALIVARY GLAND ISOGRAFTS. (E.) Hoshino, K. (Hlth. Sci. Ctr., U. Western Ontario, London, Canada) and C. D. Lin. *Europ J Cancer* 7(5):373-376, 1971.

Single submandibular glands, single parotid glands or a combination of the three major salivary glands were i.p. isografted from female BALB/c donor mice. Without further treatment, surviving graft tissues consisted only of duct-like structures throughout the 12-month investigation. Hyperplastic proliferation declined in intensity after showing active features one week after grafting and, instead of disappearing, became active again 12 months after transplantation. In each of the above mentioned grafts, isoproterenol administration, one week prior to and one week following isografting, demonstrated that hyperplastic changes, some hardly microscopically distinguishable from an adenocarcinoma, could be induced. Post-transplantation treatments with either testosterone enanthate (20 mg injected fortnightly) or estradiol valerate (1 mg or less fortnightly) could accelerate hyperplastic alterations and cause changes at six months after grafting which resemble those observed in controls at the 12 month interval. In surviving duct-like structures, acini and secretory tubules reappeared following administration of isoproterenol and testosterone resp., but no mitoses nor hyperplastic changes were observed in these reappearing cells. These phenomena suggest that only de-differentiated duct-like structures are capable of undergoing mitoses and becoming hyperplastic, but after re-differentiation, cells lose this capability.

- 1994 DEFECTIVE CONTROL OF RIBOSOMAL RNA PROCESSING IN STIMULATED LEUKEMIC LYMPHOCYTES. (E.) Rubin, A. D. (Mount Sinai Sch. Med., New York, N.Y.). *J Clin Invest* 50(12):2485-2497, 1971.

Healthy individuals and patients suffering from chronic lymphocytic leukemia (CLL) were subjected to phlebotomy. Blood obtained in this fashion was sedimented in order to isolate the lymphocytes, which were then introduced into culture. The lymphocytes *in vitro* were exposed to phytohemagglutinin (PHA) to stimulate blast formation and at various intervals were then harvested, lysed, and precipitated for collection of the RNA. The RNA, which was radioactively methylated, sedimented at 45S, 32S-28S, and 18S. It was found that the rate of 45S transcription doubled in normal lymphocytes after a one hr incubation with PHA and then continued to rise to 13 times the resting rate by 48 hr. In PHA-treated CLL cultures, an initial rise in the rate of 45S RNA transcription was detected at one hr after which 45S RNA transcription fell off to base line levels at 48 hr. Increased rates of 45S processing could be detected in normal cultures treated with PHA for 1 hr. This indicates that, in addition to an increased rate of transcription, PHA induces an even more rapid cleavage of each newly transcribed 45S molecule to 32S and 18S products. This early phenomenon was also present in CLL cultures treated with PHA for 1 hr. The initial effects of PHA on transcription and processing of 45S RNA remained intact in CLL lymphocytes.

phocytes. Nevertheless, the initial response of PHA-treated CLL lymphocytes remained abnormal in that conservation of 18S RNA failed to develop. Only at 168 hr did PHA-treated CLL lymphocytes begin to conserve 18S RNA. These findings imply that 18S conservation may exert a direct effect on the initiation of lymphocyte growth.

- 1995 KARYOTYPIC PROFILE ALTERATIONS IN EHRlich ASCITES TUMOUR CELLS DURING DEVELOPMENT OF RESISTANCE TO DAUNORUBICINE. (E.) Hasholt, L. (Inst. Path., Commun. Hosp., Copenhagen, Denmark), J. Visfeldt and K. Dano. *Acta Path Microbiol Scand* 79:665-675, 1971.

Karyotype determinations were made on a wild Ehrlich ascites tumor and on a subline which was made resistant to daunorubine (DNR) by long-term treatment with this drug. During the development of resistance to DNR, karyotypic alteration occurred, with a change from near-tetraploidy to hyperdiploidy and the appearance of marker chromosomes which were not found in the original tumor. The resistance was gradually lost on cessation of DNR treatment. A tumor subline which, after having been resistant, had become sensitive again, presented a karyotype comparable to the original tumor. Another tumor which had partially lost its resistance, was composed of a mixture of cells with karyotypes characteristic either of the sensitive or of the resistant tumor. The loss of resistance is believed to be caused by abundant growth of sensitive cells present in the resistant tumor.

- 1996 THE ANIONIC NATURE OF SARCOMA 180 CELL SURFACES, AND SENSITIVITY TO 4,4'-DIACETYLDIPHENYLUREA-BIS(GUANYLHYDRAZONE). (E.) Weiss, L. (Roswell Park Mem. Inst., Buffalo) and M. T. Nakala. *Cancer Res* 31(10):1369-1372, 1971.

A study undertaken to explore possible correlations between the anionic nature of the surfaces of two sublines of sarcoma 180 cells and the sensitivity of these cells to 4,4'-diacetyldiphenylurea-bis(guanylhydrazone)-dimethane sulfonate (DDUG) is described. The electrokinetic surface of one of the two lines of sarcoma 180 cells was resistant to DDUG while that of the other cell line was DDUG-sensitive. The net negative charges of the two cell lines were not significantly different and neither were the respective contributions of the two cell lines to cell surface negativity of bound anionic groups susceptible to neuraminidase or RNase. The sensitivity of the DDUG-sensitive sarcoma 180 cells to DDUG was altered by predigestion with neuraminidase or RNase; these two enzymes made DDUG-sensitive cells two and three times more resistant, resp., to DDUG. The response of the DDUG-resistant cells was not affected by enzyme treatment.

- 1997 STUDIES ON MALIGNANT TUMORS AND ANEMIA. REPORT 14. THE INFLUENCE OF THE ANEMIA-INDUCING SUBSTANCE FROM PLACENTAL TISSUE ON THE LIFE

SPAN OF THE RABBIT ERYTHROCYTE AND THE RETICULOENDOTHELIAL SYSTEM. (Jap.) Shimano, M. (Hirosaki U., Sch. Med., Japan). *Hirosaki Med J* 23(1):23-42, 1971.

Experiments were performed to clarify the mechanism of anemia which regularly occurs in patients with malignant neoplastic diseases. The anemic inducer P-62 in the placental tissue and the mucoprotein obtained from the gastric juice and tissue and serum obtained from gastric cancer patients are similar biochemically and immunologically, and seem to act in the same manner. P-62 is obtained by barium acetate ethanol separation of 60% v/v ethanol from a placenta fraction; the supernatant liquid is further separated by ammonium sulfate total saturation. Viability of rabbits' erythrocytes in the reticuloendothelial system was studied by tracing radioactively labelled ( $^{51}\text{Cr}$ ) erythrocytes mixed with P-62 and injected into rabbits' veins. The erythrocytes of control rabbits had apparent half lives of 9.6 to 14 days, averaging at 11.8 days. Those under the influence of P-62 had 4.5- to 12.8-day half lives, averaging at 9.1 days. The viability of erythrocytes decreased considerably when P-62 was used, radically increasing the radioactivity in the reticuloendothelial organs, especially in the spleen. A significant difference was apparent within 12 hours. On the other hand, when the 40% v/v ethanol fraction (P-40) was mixed with the same amount (0.02 mg/kg) of P-62 and mixed with rabbits' erythrocytes *in vitro*, the half life of the erythrocytes remained approximately the same as that of the control rabbits. This indicates that P-40 is antagonistic toward P-62 and acts as an inhibitor of the anemia inducing P-62.

1998 CYTOPATHOGENIC EFFECT OF HUMAN LEUKEMIC LEUKOBLASTS ON CULTURED FIBROBLASTS *IN VITRO*: CORRELATION WITH THE STIMULATING EFFECT OF LEUKOBLASTS *IN VITRO* ON AUTOLOGOUS LYMPHOCYTES. (Fr.) Fellous, M. (Hosp. St. Louis, Paris, France) and W. H. Fridman. *C R Acad Sci (Paris)* 273(23):2394-2397, 1971.

Leukemic leukoblasts capable of stimulating lymphocytes also have a cytopathogenic effect on certain fibroblasts under conditions of co-cultivation favoring cellular fusion. Leukoblasts which do not stimulate autologous lymphocytes *in vitro* are not cytopathogenic. Leukoblasts from 16 patients suffering from severe leukoblastic leukemia were isolated from defibrinated blood in the presence of plasmagel. Cellular suspensions with over 90% leukoblasts were frozen in the presence of dimethylsulfoxide and kept at  $-196^{\circ}\text{C}$  in liquid nitrogen. The *in vitro* transformation of autologous lymphocytes taken from leukemic patients in remission was determined by measuring the incorporation of tritiated thymidine from the fifth day of cultivation on in the presence of autologous thawed-out leukoblasts. The results revealed that ten of the 16 suspensions of leukemic cells stimulated autologous lymphocytes. The same leukoblasts were co-cultivated *in vitro* with two lines of human fibroblasts (the heteroploid D 98 AH<sub>2</sub> strain and the diploid 109 strain) using the Davidson technique favoring cellular fusion. Cellular

fusion was induced by treatment with UV radiation-inactivated Sendai virus. In the strain D 98 AH<sub>2</sub> cytopathogenic modifications appeared 48-72 hours after transplantation: cell volume increased, the cytoplasm cleared up, and on the fourth day cellular density decreased in comparison with control cultures. In the diploid 109 strain of fibroblasts this cytopathogenic effect was not observed. The close correlation between the stimulating effect of leukoblasts on autologous lymphocytes and cytopathogenicity suggests that both phenomena have the same cause. A metabolite, an enzyme, or an infectious agent producing an antigen, located within certain leukoblasts, or a viral or bacterial agent contaminating the blood of certain leukemic patients, could cause both phenomena.

1999 KINETICS OF PROLIFERATION IN HUMAN TUMOR CELLS. (Jap.) Shirakawa, S. (Kyoto U.). *Jap Arch Intern Med* 18(8):319-330, 1971.

A review of studies on kinetics of proliferation in human tumor cells is presented and the author's observations on the human melanoma are reported. Four secondary melanomas and one benign nevus, diameters of which were approximately 1 cm, were sampled from a 66 year old female who had received 8.5 mC of  $^3\text{H}$ -TdR i.v. 12 hours earlier. From the autoradiographic analysis the following values were obtained: labeling index (LI) 4.5-6.2%; mitotic index (MI) 0.43-0.59%; mean grain count (MGC) 31.9-40.3; and labeled mitoses 54-63%. The values for the benign nevus were: 0.43% (LI), 0.08% (MI) and 9.7 (MGC). The second patient (a 70 year old female) was given 10 mC of  $^3\text{H}$ -TdR and the sample melanomas were taken at various times (0-14 days). The durations of G<sub>2</sub>-phase and S-phase and the grain count halving time were determined graphically to be five hours, 20 hours and 6-7 days, resp. The third patient (a 49 year old female) received 3 mC of  $^3\text{H}$ -TdR every day for 20 days. Only 70% of the malignant tissue cells were labeled. The application of various methods to determine cell cycle time (Tc) and growth fraction (GF) was discussed. It was suggested that Tc and GF for the human melanoma cells were three days and 20-30%, resp.

2000 ERYTHROPOIETIC EFFECT OF PLASMA FROM PATIENTS WITH ADVANCED CANCER. (E.) Firat, D. (Long Island Jewish Med. Ctr., Jamaica, N.Y.) and J. Banzon. *Cancer Res* 31(10):1353-1359, 1971.

The erythropoietic effect of plasma (EEP) from anemic and nonanemic patients with various cancers was determined by increase in percentage of incorporation of injected  $^{59}\text{Fe}$  (0.5  $\mu\text{Ci}$  in 0.5 ml of 0.9% NaCl solution) into circulating RBC's of protein-deprived CF<sub>1</sub> adult female mice in 48 hr. For each experiment, 0.9% NaCl solution controls were included. In 14 anemic patients with lymphoma or leukemia and 12 anemic patients with solid tumors, EEP was significantly reduced ( $8.7 \pm 2\%$  and  $9.2 \pm 2.4\%$ , resp.) compared to 12 normal plasmas ( $15.4 \pm 1.7\%$ ,  $p < 0.001$ ) but was increased compared to 0.9% NaCl solution



controls ( $2.6 \pm 2.1\%$ ,  $p < 0.001$ ). In contrast, EEP in 8 nonanemic patients (4 lymphomas or leukemias and 4 solid tumors) was similar to normal controls ( $16.2 \pm 2.8\%$  and  $14 \pm 1.9\%$ , resp.) but was significantly different from their anemic counterparts ( $p < 0.001$ ). No significant differences in EEP were found among diagnostic groups by sex or between those with or without evidence of bone marrow infiltration. Age did not influence the results. It is concluded that erythropoietin level of plasma in anemic cancer patients is reduced. Whether utilization of erythropoietin or its precursors by the tumor tissue or a change in its renal excretion (rather than decreased production) is responsible cannot be stated since kinetic studies were not performed.

- 2001 CYCLIC AMP-MEDIATED STIMULATION BY CALCIUM OF THYMOCYTE PROLIFERATION. (E.) MacManus, J. P. (Nat'l. Res. Counc. Canada, Ottawa) and J. F. Whitfield. *Exp Cell Res* 69:281-288, 1971.

Varying the extracellular calcium concentration between 0.5 and 1.0 mM had no effect on the proliferation of rat thymocytes *in vitro* but doses over 1.0 mM increased cell proliferation and the intracellular concentration of cyclic AMP. Imidazole inhibited the calcium's mitogenic action. Phosphodiesterase activity was inhibited by caffeine which sensitized thymocytes to calcium's mitogenic activity. The thymocyte proliferation was stimulated by caffeine alone, which also caused a rise in cellular cyclic AMP content. A reduction in the activity of cyclic AMP-phosphodiesterase was produced by mitogenic levels of calcium. These findings indicate that calcium is the physiological equivalent of caffeine.

- 2002 CHROMOSOMAL CONTROL OF REVERSION IN TRANSFORMED CELLS. (E.) Hitotsumachi, S. (Weizmann Inst. Sci., Rehovot, Israel), Z. Rabinowitz and L. Sachs. *Nature* 231(5304):511-514, 1971.

Direct evidence is presented that the expression (E) or suppression (S) of malignancy of transformed properties depends on the balance between chromosomes with E and S factors. The chromosome groups that contain these types of chromosomes were identified by the use of revertants from transformed cells with different degrees of suppression of transformed properties. Eight variants with a reversion of properties of transformed cells were examined together with normal and transformed cells for their properties *in vitro*. Reversion in these variants was not associated with a loss of the virus genome. The cells were tested *in vivo* for their ability to form tumors after their subcutaneous inoculation into adult animals, and *in vitro* for their saturation density, cloning efficiency in liquid medium and soft agar, and the percentage of colonies at  $41^\circ\text{C}$ . The variants were then grouped on the basis of their degree of suppression of transformed properties. The karyotypes of the variants and of normal and transformed cells were studied. From this it was possible to show the number of chromosomes related to the degree of expression and the

variant group in which they were present. Transformation in the polyoma transformed cells was associated with an increase in the number of chromosomes with E which established an excess of E over S. Reversion in the subdiploid variants was associated with a specific chromosome loss which resulted in an excess of S over E. This excess was sufficient to suppress the transformed properties, in spite of maintenance of the viral genome in reverted cells. It was suggested that the treatment of cells with agents which change the chromosome balance so as to produce an excess of S may be of value in tumor therapy.

- 2003 ON CARCINOMA GROWTH AND VASCULAR SUPPLY: A STUDY OF MOUSE MAMMARY TUMOR STRAIN MTG-B. (E.) Jirtle, R. (U. Wisconsin Med. Sch., Madison) and K. H. Clifton. *Proc Soc Exp Biol Med* 138(1):267-269, 1971.

Young adult mice of the C3BF1/Wr and BC 3F1/Wr strains bearing MTG-B mammary tumors received injections of  $^{59}\text{Fe}$ -labeled red blood cells. Reference blood samples were drawn one hour later and the tumors were excised and cleaned of nonviable tissue. The functional vascular spaces of 190 such tumors were then calculated on the basis of radioactivity measurements. The relative vascularity was found to be related to tumor mass with a value of  $1.5 \times 10^{-2}$   $\mu\text{l}$  blood volume/mg viable tumor tissue.

- 2004 PITUITARY TUMOURS IN MICE WITH HYPOTHALAMIC LESIONS. (E.) Moll, J. (Med. Fac., Rotterdam, Netherlands). *Neuroendocrinology* 8(5):317-320, 1971.

The occurrence of pituitary tumors was studied in C57 black mice which were either sham operated and radiothyroidectomized or which received surgical anterior hypothalamic lesions and subsequent radiothyroidectomy. Although tumorous enlargement was seen in both groups, pituitary weight was relatively less in the surgically-lesioned mice. The tumors of control and experimental animals were histologically the same. It was considered that an intact hypothalamic regulatory mechanism was necessary for maximal pituitary response to demands for increased thyrotrophin production.

- 2005 ABDOMINAL TUMORS IN CHILDHOOD. (Sp.) Tous-saint-Aragon, E. (Children's Hosp., Mexico City), M. Salan-Martinez and C. Sarinana. *Gaceta Med Mex* 102(5):495-510, 1971.

Anatomo-pathologic material from surgical and necropsy specimens accumulated at the Children's Hospital of Mexico City between the years 1943 and 1970 is reviewed. Of 744 abdominal neoplasms 256 were located in the digestive tract, 219 were kidney tumors, 91 were tumors of the female genital apparatus, 61 were adrenal gland tumors, 49 were liver tumors and 68 were classified as miscellaneous neoplasia. The

colon constituted the main site of neoplasia of the digestive tract, whereas the small intestine was second in terms of incidence but first in terms of malignancy. Malignant nephroblastoma constituted the main category of malignant neoplasia during the first five years of life. It was thought to be derived from the metanephric blastoma during various stages of fetal development. Nephroblastoma presented adenosarcomatous, adenomyosarcomatous, adenocarcinomatous or mesenchymal structures; glomerulotubular structures were also frequent. Neuroblastoma, another malignant neoplasm of embryonal origin derived from the sympathetic nervous system, appeared to be most frequent during the first two years of life; its main site was the adrenals. Primary malignant tumor of the liver occurred mainly during the first two years of life and was third in incidence among the malignant abdominal tumors. Histologically, the fetal variety of hepatic neoplasia appeared to be more frequent than the anaplastic neoplasms. Retroperitoneal teratoma constituted the bulk of the neoplasms referred to as miscellaneous.

- 2006 BIOCHEMICAL AND TISSUE CULTURE STUDIES OF TRANSPLANTABLE MOUSE HEPATOMAS H-4, H-6, AND BW7756. (E.) Thomas, P. E. (Roche Inst. Molec. Biol., Nutley, N.J.) and J. J. Hutton. *J Nat Cancer Inst* 47(5):1025-1031, 1971.

Transplantable mouse hepatomas (BW7756, H-6, and H-4) from three genetically diverse inbred strains of mice (C57L/J, A/J, and C3Heb/FeJ) were examined both as to the levels of several enzymes and as to their behavior in tissue culture. The activities of phenylalanine hydroxylase, arginase, aminopyrine N-demethylase, glucose-6-phosphatase, aminolevulinic acid (ALA) synthetase, and aminolevulinic acid (ALA) dehydratase were investigated. It was found that glucose-6-phosphatase levels were similar in all three hepatomas, while arginase levels were not detectable at all. Phenylalanine hydroxylase was present in both BW7756 and H-4 hepatomas, but was absent in H-6 hepatoma; and aminopyrine N-demethylase was present in all three hepatomas, but at a very low activity. Only ALA synthetase and ALA dehydratase were discovered to be functionally related in all of the hepatomas. Mice bearing hepatomas were treated with the porphyrinogenic chemical 3,5-diethoxycarbonyl-1,4-dihydro-2,4,6-trimethylpyridine (DDC). It was determined colorimetrically that ALA synthetase activity increased three- to six-fold in the parts of the liver not affected by hepatoma although synthetase activity could not be detected in the hepatomas. All three hepatoma lines had similar fibroblast-like cells in culture, while the epithelial-like cells which resembled hepatocytes were the same in lines BW7756 and H-4. BW7756 and H-4 cultures showed no porphyrin accumulation when DDC was added *in vitro*; however, porphyrins did accumulate when ALA was added. It is suggested that most enzymes of the porphyrin pathway except ALA synthetase are present in hepatoma cells, particularly in the lines BW7756 and H-4.

- 2007 THE DETERMINATION OF OESTRADIOL RECEPTORS IN HUMAN MAMMARY CARCINOMAS. (Ger.) G6rlich, M. (German Acad. Sci., Berlin), and E. Heise. *Arch Geschwulstforsch* 38(2):139-149, 1971.

The estradiol receptor activity of human mammary carcinoma was studied on 38 surgically removed tumors. Estradiol incorporation in tissues consists of a specific bond to receptors and a nonspecific bond to albumin-like proteins. The carcinoma was regarded as estradiol sensitive when decreased estradiol incorporation was observed in the presence of antiestrogen using Jensen's method. Jensen's receptor activity determination method was applied on tissues from 38 cases of radical operation or mastectomy through the comparison of incubation (90 min) with and without antiestrogen (0.03 ml of U-1110A) in the presence of glucose and 0.02 ml of estradiol. Estradiol sensitivity was found in eight of the 38 cases (21.0%). Regional lymph node metastasis was found in seven of the eight hormone lymph node sensitive cases. Metastasis was seen in 28.7% of the 108 lymph nodes examined in the hormone-sensitive group; the corresponding percentage in the nonsensitive group (510 lymph nodes investigated) was 34.3%. In two of the three cases where the receptor activity of primary tumor and lymph node metastasis could be compared, the primary tumor was found to be no longer sensitive.

- 2008 CYTOGENETIC OBSERVATIONS IN CHILDREN WITH LEUKEMIA. (E.) Higurashi, M. (Dept. Pediat., U. Tokyo, Japan), Y. Nakagome, I. Matsui, and M. Naganuma. *Paediat Univ Tokyo* 18:36-40, 1970.

Chromosomal patterns of five male patients with chronic myelocytic leukemia and 43 male and female patients with acute leukemia are reviewed in an attempt to determine the frequency of chromosomal changes, to study possible association between abnormalities and the type of leukemia, and to correlate abnormalities with clinical features of chronic myelocytic leukemia. Two of the five cases of chronic myelocytic leukemia had a small acrocentric Philadelphia (Ph<sup>1</sup>) chromosome. Two cell lines were derived from one of the three patients without the Ph<sup>1</sup> chromosome, a diploid line with a normal karyotype and a pseudodiploid line missing two chromosomes from the E group and having two extra ones in the C and D groups. Five of 13 acute leukemia cases had Down's syndrome. Of these, all had promyelocytic leukemia. Only two of these five cases showed chromosome abnormalities other than those associated with Down's syndrome. Of the 43 cases with acute leukemia 28 showed a normal diploid karyotype. The abnormal karyotypes were observed more frequently in the myelocytic form of acute leukemia than in the stem cell form. There were no marker chromosomes present in the abnormal cases. Groups C and G showed the highest incidence of abnormalities. Clinical and hematologic findings of the five chronic myelocytic leukemia cases were compared with the features of the two types of



myelocytic leukemia observed by Bloom (i.e., adult type and juvenile type). Ph<sup>1</sup>-positive cases were all found in the age group over three years and Ph<sup>1</sup>-negative cases were all less than two years of age.

- 2009 DIFFERENCE IN TOPOLOGY OF NORMAL AND TUMOUR CELL MEMBRANES SHOWN BY DIFFERENT SURFACE DISTRIBUTIONS OF FERRITIN-CONJUGATED CONCAVALIN A. (E.) Nicolson, G. L. (Salk Inst. Biol. Stud., La Jolla, Calif.). *Nature New Biol* 233:244-246, 1971.

To determine whether cell surface architecture changes during transformation, BALB/c 3T3, a normal mouse fibroblast cell line, and SV40-transformed BALB/c 3T3 (SV3T3) cells were examined for differences in the distribution of concanavalin A (Con A) binding sites on their membranes. Electron micrographs of cells treated with purified ferritin-conjugated Con A (Fer-Con A) or ferritin-conjugated antibodies were studied using a preparation enabling a resolution of approximately 200 Å. The distribution of Fer-Con A on 3T3 cell surfaces is essentially random with few clusters of bound agglutinin. Fer-Con A is distributed randomly in clusters on SV3T3 membranes. The clusters are sometimes restricted to a large region and may also be associated with villus-like projections. Estimates show that the cell surface area of SV3T3 cells is about half that of normal 3T3 cells. Thus, the increased density of Con A binding sites on SV3T3 is due to crowding of previously existing sites, since the absolute number of sites is the same as on normal 3T3 surfaces. Apparently, the total number of agglutinin sites and their topographic distribution are both factors in producing agglutination of cells. Fer-Con A staining of trypsinized 3T3 cells shows increased clustering of agglutinin sites similar to the pattern normally seen on SV3T3 surfaces. This change is reversible, as is the increased cell agglutination which accompanies it. It is concluded that cell surface changes do occur in conjunction with transformation.

- 2010 GRANULAR CELL MYOBLASTOMA: AN ELECTRON MICROSCOPIC AND CYTOCHEMICAL STUDY ILLUSTRATING THE GENESIS OF GRANULES AND AGING OF MYOBLASTOMA CELLS. (E.) Sobel, H. J. (Beth Israel Hosp., Passaic, N.J.), E. Marquet, E. Avrin and R. Schwarz. *Amer J Path* 65(1):59-78, 1971.

The lysosomes, endoplasmic reticulum, mitochondria, Golgi apparatus and membranes of seven typical granular cell myoblastomas were studied with the electron microscope. All seven were found to be identical according to these parameters. The authors describe two classes of granules in the cytoplasm of myoblastomas. Small granules resemble lysosomes morphologically but do not stain with typical lysosome markers. Apparently they are derived from the Golgi apparatus. The large granules, which are lysosomes, are apparently of two types. All contain acid phosphatase and a few possess thiolacetic acid esterase

activity. Morphologic evidence is presented indicating that myoblastoma cells undergo an aging process. It is also concluded that myoblastomas are tumor-like lesions which are of Schwann cell origin through either a reactive cellular response or through true neoplasia.

- 2011 NUCLEAR RNA OF NORMAL AND LEUKAEMIC HUMAN LEUCOCYTES. (E.) Malec, J. (Inst. Haematol., Warsaw, Poland), M. Wojnarowska and L. Kornacka. *Haematologia* 5(1-2):25-36, 1971.

A comparative study of some nuclear RNA structural and metabolic features of lymphocytes and granulocytes of normal subjects and of patients with chronic lymphocytic and chronic myelogenous leukemia was performed. Leukocytic nuclei *in vitro* were isolated and fractionated into four groups of subnuclear components: nuclear sap; a chromatin fraction divided into high (cytosine or guanine rich) or low (adenine or uracil rich) molecular weights, and a nuclear residue. Chromatographic and pulse labeling analyses were then done on each component. The RNA present in the chromatin of all kinds of white cells consisted of two fractions which differed considerably in their base composition; the nucleotide composition of newly synthesized RNA in the nucleoli and nuclear residue was different in the normal, myelogenous, and lymphocytic type cells. The myelogenous cell type and the normal granulocyte had a high guanine-cytosine content, while the normal and malignant lymphocytic cell types were adenine-uracil rich. Upon further experimentation it was determined that the general pattern of labeling of various nuclear RNA was similar in all white cells studied. The specific activity was highest in the RNA of nucleoli or of the nuclear residue fraction, was next highest in the chromatin of low molecular weight, and was lowest in the chromatin of high molecular weight or in the nuclear sap RNA.

- 2012 SPONTANEOUS NEOPLASMS IN GERM-FREE BALB/cP<sub>1</sub> MICE. (E.) Smith, C. S. (U. Utah Coll. Med., Salt Lake City) and H. I. Pilgrim. *Proc Soc Exp Biol Med* 138(2):542-544, 1971.

This paper presents data indicating that the germ-free state has little or no effect on spontaneous tumor development in animals. Specifically, the germ-free BALB/cP<sub>1</sub> mouse subline derived from BALB/cAnHf was studied over a two-year period. In 67 aging mice, it was found that there were 14 primary lung tumors, five reticular neoplasms, four angiomas, two hepatomas, two squamous cell carcinomas, two adrenal cortical carcinomas, and a transplantable myoepithelioma. Of the 52 breeding female mice, two were found to have mammary carcinoma and one had an ovarian carcinoma. In addition, 11 non-neoplastic spontaneous lesions were noted. It was concluded that there was little or no difference in the incidence of spontaneous neoplasms between that reported in conventional BALB/c mice and that reported in this study.

- 2013 ACTIVATION OF SPONTANEOUS MURINE LEUKEMIA VIRUS-RELATED ANTIGEN BY LYMPHOCYTIC CHORIOMENINGITIS VIRUS. (E.) Oldstone, M. B. A. (Scripps Clin. Fdn., La Jolla, Calif.), T. Aoki and F. J. Dixon. *Science* 174(4011):843-845, 1971.

Inbred strains of NZB mice and their hybrids with NZW mice, having a high leukemia incidence and carrying large amounts of Gross virus, and NZW and C57BL/6 mice, having a low leukemia incidence and carrying little or no Gross virus, were either chronically infected *in vivo* with lymphocytic choriomeningitis (LCM) virus or were maintained as controls. Gross soluble antigen (GSA) was detected in the plasmas of 84% of the NZW mice, 90% of the NZB mice and the hybrids, and 60% of the C57BL/6 mice; on the other hand, the percentage of GSA in the control animals was less than or equal to 5% in all groups. To eliminate the possibility of Gross viral contamination, three supportive experiments were carried out. First, LCM cloned, plaque purified viruses were inoculated into NZW mice at birth. At 3 months of age, 57 to 70 percent of these mice had GSA in their circulation, as compared to less than 3 percent of noninfected controls. Second, LCM virus passed through brains of NZW mice was incubated with (W/Fu x BN)<sub>F1</sub> rat serum to W/Fu (C58NT)D that neutralizes Gross leukemia viruses, for 30 minutes at room temperature and inoculated into mice. The increased incidence of GSA persisted. A similar incubation with a guinea pig antiserum to LCM did alter the incidence. Third, electron microscopic examination of pooled LCM viruses that had undergone brain passage failed to reveal any oncornavirus particles. Finally, *in vitro* studies of mouse embryo fibroblasts inoculated with LCM indicated that GSA would be produced; however, mouse embryo fibroblast cultures alone failed to produce any antigen. The implications of these results are that the phenotypic expression of the Gross viral genome may be activated by a chronic nononcogenic virus which can be vertically transmitted and that oncornavirus participates in immunologically induced disease by virtue of its interaction with sensitized cells or antibodies (or both) produced by the host.

- 2014 TWENTY-FOUR-HOUR VARIATIONS IN DNA SYNTHESIS OF A FAST-GROWING AND A SLOW-GROWING HEPATOMA: DNA SYNTHESIS RHYTHM IN HEPATOMA. (E.) Nash, R. E. (Fac. Med. Sci., Nat. U. La Plata, Argentina) and J. M. Echave Llanos. *J Nat Cancer Inst* 47(5):1007-1012, 1971.

The 24-hour variations in DNA synthesis of a slow-growing hepatoma (SS1H) and a fast-growing hepatoma (SS1K) were studied. Host C3H-S male mice were injected interscapularly with cell suspensions from both tumors. The mice were grafted with both hepatomas several weeks later and standardized for periodicity analysis (*sic*). After several more weeks groups of mice were given tritiated thymidine and sacrificed at four hour intervals. The tumors were excised and representative samples were fixed and autoradiographed. Hepatoma SS1H had a higher value for DNA synthesis during the dark period (4 A.M.

peak) than during the light period (1 P.M. trough); hepatoma SS1K had insignificant oscillations during the 24 hour period. All the experiments indicated that DNA synthesis was higher during the dark period, while mitotic activity was higher during the light period. A comparison of the present results for 24-hour variations in DNA synthesis of both tumors with those of 24-hour variations in mitotic activity indicates that circadian variations in DNA synthesis of hepatoma SS1H could be correlated with those previously reported in mitotic activity of the same tumor type. In hepatoma SS1K, however, the range of percent variation of DNA synthesis and mitotic activity around the 24 hour mean was lower than in hepatoma SS1H. In SS1K, the rhythmic character of the variation of the two parameters was apparent only in mitotic activity.

- 2015 PLOIDY FLUCTUATIONS OF MOUSE PLASMA-CELL NEOPLASM MSPC-1 DURING SERIAL TRANSPLANTATION. (E.) Moriawaki, K. (Natl. Inst. Genet. Misima, Japan), H. T. Imai, J. Yamashita and T. H. Yosida. *J Nat Cancer Inst* 47(3):623-637, 1971.

An explanation was sought for the increased frequency of tetraploidy in successive transplant passages of the MSPC-1 plasma-cell neoplasm of BALB/c mice. It had been suggested that tetraploid tumor cells which had lost their transplantation antigens were subject to immunoselection by the tumor host. The antigenic character of the MSPC-1 in syngeneic mice, and the effect of host conditions on ploidy changes in MSPC-1 tumor cells, were investigated. Neither destruction of the host's immune-response mechanism by pretreatment with  $\gamma$ -rays (400 R), nor double inoculation of diploid and tetraploid tumor cells to a single host, confirmed that the immunoselection mechanism of hosts directly affected the increase of tetraploid cells. It was thought that some factors within the tumor cells had an essential function in facilitating tetraploidy. Changes in tumor cell populations during serial transplantation were also observed. During serial passage three marker chromosomes appeared additively. These markers occurred with different frequencies in different passages of cells; two of the markers were seen in diploid cells as well as in tetraploid cells. The appearance of a new cell population with specific marker chromosomes was always followed by an increase of tetraploids. Tetraploidy of plasma cells has been thought to reflect certain steps of maturation. If this is the case, then the increased frequency of tetraploids might represent the maturation of each new cell population.

- 2016 SURFACE STRUCTURE OF THE PLASMA MEMBRANES ISOLATED FROM RAT LIVER AND ASCITES HEPATOMA. (E.) Seki, S. (Okayama U. Med. Sch., Japan), S. Omura and T. Oda. *Gann* 62(2):89-94 (and Plates IX-XIV), 1971.

Electron microscopic studies were conducted on plasma membranes isolated from rat liver and AH-130 strain of rat ascites hepatoma. Negative staining



with potassium phosphotungstate revealed the same type of distribution of fine 20 to 30 Å granules on the membranes of both types of cells. Pretreatment of the normal plasma membranes at 37°C for one hour followed by negative staining sometimes showed a pattern of packed polygonal facets (primarily hexagonal) of about 60 to 70 Å in size. In contrast, the hexagonal pattern was observed on the surface of the hepatoma plasma membranes in only a single case when these membranes were similarly pretreated with temperature. When the plasma membranes were digested with 0.2% trypsin at 37° about 30% of the total protein was solubilized. Acetone treatment of the liver plasma membranes extracted about 70% of lipid inorganic phosphorous. Electron-microscopic examination of membranes treated with trypsin or acetone revealed that the temperature-dependent hexagonal pattern was still observed in the trypsin-treated membrane, but not in the acetone-treated. This result suggests that the difference between the membranes of rat liver cells and ascites hepatoma cells in respect to the temperature-dependent appearance of the hexagonal pattern is mainly due to the difference in the quantity and/or quality of lipid between these membranes.

- 2017 THE SIGNIFICANCE OF LYSOZYME ESTIMATIONS IN ACUTE MYELOID AND CHRONIC MONOCYTIC LEUKAEMIA. (E.) Catovsky, D. (Royal Postgrad. Med. Sch., London, England), D. A. G. Galton and C. Griffin. *Brit J Haemat* 21:565-580, 1971.

Lysozyme (systematic name: mucopolysaccharide N-acetyl muramyl hydrolase) has been found in the serum and urine of patients suffering from leukemia. The following study was done to confirm this finding and to assess the value of lysozyme estimation in classifying acute myeloid leukemias. Seventeen patients suffering from acute myeloid leukemia were first classified into one of three categories: acute myeloblastic leukemia (AMBL), acute myelomonocytic leukemia (AMML), or acute monoblastic-monocytic leukemia (AMoL). These patients, six patients with chronic monocytic leukemia (CMoL), and thirty healthy normal controls were used as sources of serum and urine specimens. The turbidimetric method was used for analysis of the lysozyme content of the specimens. Serum levels were normal in all the AMBL cases, moderately increased in five AMML cases, and very high in two AMML cases and in all AMoL cases except one. A correlation was also found between the absolute monocytic count in the blood and the lysozyme levels, with higher counts generally corresponding to higher lysozyme concentrations. The amounts of lysozyme excreted in the urine exhibited basically the same pattern as the serum estimations: the levels were normal in AMBL, and increased in all but a single case of AMML, AMoL, and in all five cases of CMoL tested. Serum lysozyme was estimated repeatedly during the treatment courses of seven AMML and AMoL patients. In four patients, serum lysozyme levels fell when the disease remitted and rose again during relapse. In one case serum and urinary lysozyme levels dropped to normal from initial high levels as remission set in, and remained normal during relapse. In two patients lysozyme

levels fell as the monocyte count diminished although there was no remission. The prognostic value of lysozyme estimations alone remains controversial, but estimations considered relative to morphologic and hematologic factors permit a more precise classification of AML and have helped in the management of patients.

- 2018 CYTOCHEMICAL INVESTIGATION OF DNA SYNTHESIS OF TUMOR CELLS. (Ger.) Lederer, B. (Path. Inst., U. Innsbruck, Austria), G. Mikuz and W. G. Moore. *Acta Histochem* (suppl. 7):247-251, 1971.

A combination of an autoradiographic method and a cytophotometric method was used to determine the incorporation rate of <sup>3</sup>H-thymidine into the DNA of the cell nuclei of an Ehrlich ascites tumor at different periods of the S-phase. It was found that the rate of incorporation of this precursor was variable, increasing over the course of the S-phase. Some evidence was obtained for a DNA synthesis initiation phase occurring at the beginning of the S-phase, associated with a slow labeling process and low silver grain counts. A low DNA synthesis activity period occurring at the end of the S-phase was also observed.

- 2019 THE FINE STRUCTURE OF BASAL CELL ADENOMA OF THE SALIVARY GLAND: A CONTRIBUTION ON CELL DIFFERENTIATION IN SALIVARY GLAND TUMORS. (Ger.) Hubner, G. (Path. Inst., Cologne U., Germany), O. Kleinsasser and H. J. Klein. *Virchow Arch Path Anat* 353(4):333-346, 1971.

Ultrastructural studies of seven human parotid gland adenomas revealed differentiation of the epithelial cell structure. The tumor cells appeared to contain large amounts of chaotic fine fibrillar structures of yet unknown origin and function and were poor in organelles. The differentiated epithelial tumor cells seemed to contribute to the generation of interstitial fibrils and of the basic membrane-like substance, leading to an edematous aspect of the tumor stroma. An elastic substance between the epithelial layers of the tumor was one of the specific features found. The lack of myoepithelial cells in the structure of these tumors allowed them to be distinguished from mixed tumors, cylindromas and salivary gland duct carcinomas.

- 2020 DNA CONTENT OF MASTOCYTOMA CELLS IN CELL CULTURE AFTER INHIBITION OF RNA SYNTHESIS WITH 6-AZAURODINE. (E.) Burki, H. R. (Dept. Path., U. Bern, Switzerland). *Cancer Res* 31:1188-1191, 1971.

The DNA content of mastocytoma cells, selectively inhibited by 6-azauridine (AzUR) in the presence of DNA precursors, deoxycytidine (CdR) and thymidine (TdR) was determined by microfluorometry. Suspension cultures of a transplantable murine mast cell tumor (cell line P-815-X2) were used. Results indicated that blocking RNA syntheses with AzUR + CdR

+ TdR caused a depletion of cells in S- and G<sub>2</sub>-phase and an accumulation of G<sub>1</sub>-phase cells. Because the increase in cell density in cell cultures treated with AzUR, CdR and TdR was similar to that of control cultures, it was concluded that the major portion of S- and G<sub>2</sub>-phase cells may proceed more or less normally through mitosis despite substantial inhibition of RNA synthesis. It was concluded that the inhibition of RNA synthesis with a combination of 6-azauridine, deoxycytidine, and thymidine delayed the entry of G<sub>1</sub>-phase cells into the S-phase of the cell cycle.

2021 A CHROMOSOME SURVEY ON TISSUE CULTURE CELLS DERIVED FROM NASOPHARYNGEAL CANCER. (E.)

Utsumi, K. R. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan) and T. O. Yoshida. *Gann* 10:291-295, 1971.

Karyotype analyses, performed on 13 strains of tissue culture derived from nasopharyngeal cancer patients, are described. A modal number of 46 chromosomes predominated in 12 of 13 strains; the exception was one strain (NPC-37) with a modal number of 45. Karyotype analyses made on those cells with a modal chromosome number of 46 in each strain revealed no apparent difference from the normal diploid karyotype. Loss of the Y chromosome was seen in all metaphases of the NPC-37 strain, and was responsible for the shift in the modal number in this line. In one NPC-37 cell an additional chromosome resembling trisomy C-10 was seen. It was thought that loss of the Y chromosome occurred in the cancer tissue. It was not clear whether or not tissue culture cells with the normal karyotype, found as a predominant fraction of the cell population, were derived from neoplastic tissue or stroma.

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Buch, L. (Molec. Biol. Inst., U. California Los Angeles), D. Streeter, R. M. Halpern, L. N. Simon, M. G. Stout and R. A. Smith. *Biochemistry* 11(3):393-397, 1971.

Transfer (t) RNA methylase was isolated in a cell-free preparation from the human KB tumor tissue culture line. The enzyme was then subjected to the inhibitory agent, nicotinamide, and to other inhibitory chemical analogs. It was found that nicotinamide and six other compounds (thionicotinamide, 6-aminonicotinamide, pyridine-3-, pyridine-4-, and pyridine-2-carboxaldehyde, and 3-methylpyridine) could slow the tRNA methylation process. However, the types of inhibition were not identical for all compounds; using competitive kinetic methods, nicotinamide exhibited a mixed kind of inhibition, while a weaker type of inhibition was caused by thionicotinamide and 6-aminonicotinamide. Further studies on rat liver and W-256 tumor cell methylases using only nicotinamide yielded results similar to those using KB cells. Nicotinamide was also shown to inhibit tRNA methylases prepared from four human tumors, but was inactive against tRNA methylase obtained from normal tissues surrounding the tumors.

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 GUIBAUD, S.  
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 GUINDON, A.  
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 GULI, E.P.G.  
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 1546, 1643\*  
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 JACOBS, P.H.  
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 LAI, M.M.C.  
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 LAIHO, K.U.  
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MEYERS, B.R.  
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MICCO, P. DE  
1948  
MICHELMAYR, G.  
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MIKAYA, Z.A.  
1875\*  
MIKUZ, G.  
2018  
MILHAM, S., JR.  
1932  
MILLER, A.  
1837  
MILLER, J.F.A.P.  
1860\*  
MILLER, R.W.  
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MILLER, S.H.  
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MINTY, C.C.J.  
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MOVILEANU, D.  
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1982  
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MURRAY, D.E.  
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NAEIM, F.  
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2008  
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1719  
NAIPAUL, N.  
1804  
NAIRN, R.C.  
1846\*, 1867\*, 1868\*  
NAKAGOME, Y.  
2008  
NAKAMURA, K.  
1597, 1736  
NAKAYAMA, S.  
1666, 1667  
NASH, G.  
2139\*  
NASH, R.E.  
2014  
NASKALSKI, J.  
1517  
NATALE, N.  
1817  
NATHANS, D.  
1752  
NATHANSON, N.  
1854\*  
NATHENSON, S.G.  
1847\*  
NEELL, W.E., JR.  
1543  
NELSON, R.L.  
1535, 1591, 1661  
NELSON, V.G.  
2040\*  
NELSON-REES, W.A.  
1755  
NEMOTO, T.  
2133\*

NESBIT, M.E., JR.  
1939\*  
NEVINS, M.P.  
1556  
NEWBLERNE, P.M.  
1558  
NEZELOF, C.  
2050\*  
NG, A.B.P.  
1887  
NICOLI, J.  
1836  
NICOLSON, G.L.  
2009  
NICOLSON, M.O.  
1731  
NILSSON, K.  
1809  
NILSSON, S.  
2101\*  
NIND, A.P.P.  
1867\*, 1868\*  
NISHIDA, S.  
1754  
NISHIO, Y.  
1812  
NODSKOV-PEDERSEN, S.  
2089\*  
NOERJASIN, B.  
1833  
NOHARA, Y.  
1929  
NOMURA, S.  
1732, 1733  
NONOYAMA, M.  
1703  
NORMAN, J.L.  
2122\*  
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2111\*  
NOSSAL, G.J.V.  
1829  
NOTKINS, A.L.  
1810  
NOVIKOVA, M.A.  
2194\*  
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2191\*  
NOVOTNA, L.  
1790  
NOWINSKI, R.C.  
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NUNNA, N.G.  
2140\*  
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O'BRIEN, P.H.  
2061\*  
OBUKH, I.B.  
1840  
O'CONNOR, G.B.  
1543  
O'CROININ, P.  
2150\*  
ODA, T.  
2016  
ODILI, J.L.  
1794  
OEGREN, S.  
2163\*  
OESTHERG, G.  
2130\*  
OGATA, M.  
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OHAYON, E.  
1871\*  
OHSUGI, M.  
1826  
OKADA, S.  
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OKULSKI, J.  
2167\*  
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OLDSTONE, M.B.A.  
1832, 2013  
OLINICI, C.D.  
2065\*  
OLIVER, I.T.  
1611\*  
OLJSHANETSKAYA, A.D.  
2194\*  
OLSON, R.L.  
2060\*  
OLSZEWSKI, W.  
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OMURA, S.  
2016  
O'NEILL, R.T.  
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OPLER, L.A.  
2173\*  
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1641\*  
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1897\*, 1898\*  
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O'SHEA, J.D.  
1643\*  
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1929

OSSKI, G.  
1888  
OSTASHKOV, L.K.  
2119\*  
OTTEN, J.  
1737  
OYASU, R.  
2113\*  
OZZELLO, L.  
2099\*  
PACHALIYA, N.A.  
1875\*  
PADILLA, F.  
2078\*  
PAGANO, J.S.  
1703  
PAI, M.K.  
1804  
PAJDAK, W.  
1517  
PAKH, M.  
1838  
PALFRAMAN, J.F.  
1583  
PARKHOMENKO, I.I.  
1762  
PARMIANI, G.  
1610\*  
PARONETTO, F.  
2087\*  
PARROW, A.  
2199\*  
PARSHIN, A.N.  
2127\*  
PASHINTSEVA, L.P.  
2118\*  
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PASTAN, I.  
1737  
PATAKFALVI, A.  
1857\*  
PATTERSON, R.  
2046\*  
PAUL, D.  
1791  
PAULUZZI, S.  
1712, 1764\*  
PAVLOV, D.  
2083\*  
PAVLOVSKY, A.  
1800  
PAWELETZ, N.  
2169\*  
PAYMASTER, J.C.  
1930

PAYNE, J.E.  
2084\*  
PEDROSO, A.F.  
1557  
PEEBLES, P.T.  
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PERKINS, J.P.  
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PETERSEN, K.W.  
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1793  
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PIATKOWSKI, Z.  
2187\*  
PIESSENS, W.F.  
1990  
PILGRIM, H.I.  
1981, 2012  
PILLINGER, D.J.  
1646\*  
PINCUS, T.  
1711  
PINKERTON, H.  
1805  
PINN, V.W.  
1842\*  
PIRRO, G.  
1957  
PITARO, R.  
2031\*  
PITT, P.  
1616\*  
PLAPP, F.V.  
1652\*  
PLATONOVA, G.N.  
1629\*  
PLEWIG, G.  
1880

PODZEY, L.K.  
1604\*  
POGOSYANTS, YE.YE.  
1913\*  
POINTNER, H.  
1552  
POKROVSKY, A.A.  
1621\*  
POLLIACK, A.  
1774\*  
POLLICE, L.  
1523\*  
POLYZONIS, M.  
1553  
PONTEN, J.  
1952  
POPESCU, A.  
1548  
POPESCU, I.G.  
1862\*  
POPISIL, M.  
1879\*  
POTAPENKOVA, L.S.  
1893  
POTH, J.L.  
1664  
POTICHA, S.M.  
2113\*  
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POWELL, H.  
1506  
PRAGER, M.D.  
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PUKHALSKAYA, E.CH.  
1629\*  
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2061\*  
QASBA, P.K.  
1761  
QUADRI, S.K.  
1951  
QUATRALE, A.C.  
2098\*



RABASA, S.L.  
 1803  
 RABBISOI, G.  
 1902\*  
 RABES, H.M.  
 1560  
 RABINOWITZ, Z.  
 2002  
 RABSON, A.S.  
 1725  
 RACOVEANU, C.  
 1862\*  
 RAILEANU-MOTOIU, I.  
 1862\*  
 RAIMONDI, L.  
 1822  
 RAKUSANOVA, T.  
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 RAMADAN, M.A.-E.  
 1588  
 RANDERATH, K.  
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 1730  
 RATNAM, S.S.  
 1987  
 RAUTH, A.M.  
 1685\*  
 RAVENTOS, A.  
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 RAWLS, W.E.  
 1718  
 REAGAN, J.W.  
 1887  
 REES, K.R.  
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 REHN, M.  
 1691\*, 1928  
 REID, T.W.  
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 REIFLBERG, U.  
 1863\*  
 REINER, J.  
 1817  
 REINHARD, M.  
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 REITER, E.O.  
 2148\*  
 REMINGTON, J.S.  
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 RENZI, G.  
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 REUBER, M.D.  
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RIBACCHI, R.  
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 RICHTER, R.  
 1796  
 RICK, K.  
 2036\*  
 RIESCO, A.  
 2066\*  
 RIFKIN, D.B.  
 1747  
 RILEY, W.D.  
 1904\*  
 RINGELMANN, W.  
 1560  
 RINGERTZ, N.R.  
 1808  
 RIPPS, C.S.  
 1850\*  
 RITZMANN, S.E.  
 1683\*  
 RIVERA, G.  
 2049\*  
 ROBERT, J.-M.  
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 ROBERTS, M.  
 2046\*  
 ROBERT-VAGUE, D.  
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 RODE, H.N.  
 2170\*  
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 ROGERS, A.E.  
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 ROLLAND, J.M.  
 1867\*, 1868\*  
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 1910\*  
 ROLOVIC, Z.  
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 ROOD, J.J. VAN  
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 ROSENBERG, S.A.  
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 1686\*  
 ROSENTHAL, J.  
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 ROSENTHAL, L.J.  
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ROVERA, G.  
 1884  
 ROWE, W.P.  
 1711, 1735  
 ROYSTER, H.P.  
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 RUBIN, A.D.  
 1994  
 RUBIN, P.  
 1680\*  
 RUBIO, C.  
 2080\*  
 RUCKES, J.  
 2153\*  
 RUDNICKI, T.  
 1677\*  
 RUHL, E.  
 2126\*  
 RUIZ, F.  
 2177\*  
 RUMI, L.  
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 RUSCIANI, L.  
 1897\*  
 RUVIDIC, R.  
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 RYAN, J.P.  
 2158\*  
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 1775\*  
 SABBATH, M.  
 1567  
 SABEL, M.  
 1639\*  
 SACHS, L.  
 2002  
 SAEZ, S.  
 1978  
 SAINI, N.  
 1690\*  
 SAKAI, H.  
 1683\*  
 SAKURAI, Y.  
 1628\*  
 SALMASO, E.  
 1943\*  
 SALMON, H.  
 1871\*  
 SALWA, J.  
 1796  
 SALA, J.M.  
 1954  
 SALAMAN, M.H.  
 1801  
 SALAN-MARTINEZ, M.  
 2005

SALAZAR, H.  
 2110\*  
 SAMOILOVICH, L.N.  
 1602  
 SAN, R.H.C.  
 1596  
 SANDAKATA, K.  
 2075\*  
 SANDER, J.  
 1608\*  
 SANTAGATI, G.  
 1902\*  
 SANY, J.  
 2053\*  
 SARFATY, G.  
 1616\*  
 SARINANA, C.  
 2005  
 SARKAR, N.H.  
 1501, 1695, 1726  
 SARMA, P.S.  
 1734  
 SARTWELL, P.E.  
 1922  
 SATO, G.  
 1791  
 SATO, M.  
 1983  
 SAVULESCU, A.  
 1548  
 SAWICKI, W.  
 1753  
 SCARPA, C.  
 1906\*  
 SCERBOVA, E.N.  
 1672\*  
 SCHAEFFER, B.T.  
 1797  
 SCHAPIRA, F.  
 1949  
 SCHAPIRA, G.  
 2175\*  
 SCHARFF, M.D.  
 1806  
 SCHATZKI, P.F.  
 2106\*  
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 SCHER, C.D.  
 1755  
 SCHERRER, K.  
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 SCHIFFER, D.  
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SCHIMMER, B.P.  
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 SCHMAEHL, D.  
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 SCHMIDT, C.O.  
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 2082\*  
 SCHRIER, S.L.  
 1664  
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 2010  
 SEAMAN, E.  
 2136\*  
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 1541  
 SEIBERT, R.A.  
 1580  
 SEIDEL, H.  
 2036\*  
 SEIDLER, E.  
 1590  
 SEIDMAN, H.  
 1942\*  
 SEKI, S.  
 2016  
 SEKIYA, S.  
 1597, 1736  
 SEKIZUKA, H.  
 2104\*  
 SELEZNEV, YE.K.  
 1890  
 SELIGMANN, M.  
 1873\*  
 SELLERS, L.  
 2174\*  
 SEMAN, G.  
 1692, 1802  
 SERCARZ, E.E.  
 1837

SERRE, H.  
 2053\*  
 SETLOW, J.K.  
 1540  
 SFORZA, M.  
 1943\*  
 SHABAD, L.M.  
 1576, 1603\*  
 SHADDUCK, R.K.  
 2140\*  
 SHANI, M.  
 1919  
 SHANK, R.C.  
 1613\*  
 SHAPOSHNIKOV, D.  
 2128\*  
 SHARGEL, L.  
 1627\*  
 SHARMA, B.K.  
 2113\*  
 SHAYN, A.A.  
 1925  
 SHEAHAN, D.G.  
 1839  
 SHEIN, H.M.  
 1750  
 SHELBURNE, J.D.  
 2064\*  
 SHELDON, R.  
 1766\*  
 SHERIDAN, J.D.  
 1985  
 SHIER, W.T.  
 1798  
 SHIGEMATSU, T.  
 1697  
 SHILS, M.E.  
 1502  
 SHIMANO, M.  
 1997  
 SHIRAKAWA, S.  
 1999  
 SHISHKIN, S.S.  
 2182\*  
 SHMUNES, E.  
 1961  
 SHORE, B.  
 1820  
 SHOYAB, M.  
 2085\*  
 SHUSTOVA, M.N.  
 1602  
 SIDRANSKY, H.  
 1586  
 SIGNORELLI, C.  
 2096\*



SIGURDSON, A.	SNELL, G.D.	STEINBERG, D.
2080*	1516	2087*
SILVERBERG, S.G.	SNYDER, R.	STEINBERG, S.M.
2109*	1750	2166*
SILVERMAN, D.A.	SNYDER, S.P.	STEINDEL, H.J.
1815	1699	2036*
SIMON, K.	SOBEL, H.J.	STEINER, G.C.
1857*	2010	2116*
SIMON, L.	SOKOVA, O.I.	STEINMAN, H.G.
2053*	1913*	2098*
SIMON, L.N.	SOLOFF, B.L.	STERN, H.
2022	2078*	1527*
SIMPSON, E.	SOLYMOSS, B.	STERNBERG, S.S.
1509	1566, 1571	1532
SIMS, P.	SOMER, P. DE	STEVENS, D.A.
1533	1872*	1700
SINGAL, D.P.	SOMERS, K.	STEWART, B.W.
1804	1729	1587
SINGER, Z.	SOMOGYI, A.	STEWART, T.H.M.
1796	1566, 1571	1641*
SINKS, L.F.	SOUREK, J.	STICH, H.F.
2150*	1775*	1596
SIPERSTEIN, M.D.	SOUTHAM, C.M.	STIFFEL, C.
1968	1817	1573
SJODIN, L.	SOVOVA, V.	STOCK, J.A.
1605*	1792	1625*
SJOGREN, H.O.	SPARSHOTT, S.M.	STOCKERT, E.
1828	1555	1841
SKINNIDER, L.F.	SPIEGELMAN, S.	STOCKINGER, L.
2141*	1696, 1704	1552
SLATER, T.F.	SPIVACK, M.	STOTSKAYA, L.N.
1614*	1849*	2191*
SLESERS, A.	SPRATT, J.S.	STOUT, M.G.
1986	1954	2022
SLONINSKA, B.	SPRENT, J.	STOWELL, R.E.
1677*	1860*	2040*
SMETANIN, E.YE.	STACKHOUSE, L.	STRAAT, P.A.
1603*, 1607*	1679*	1572
SMITH, C.S.	STALSBERG, H.	STRANDBERG, J.D.
2012	1955	1723
SMITH, E.K.	STANISLAWSKI, M.	STRASSER, F.F.
2040*	1859*	1654*
SMITH, J.B.	STANLEY, A.J.	STRASSER, K.
2144*	2039*	2124*
SMITH, P.	STANLEY, E.R.	STRAZHEVSKAYA, N.B.
2057*	2097*	1976
SMITH, R.A.	STAVEM, P.	STREETER, D.
2022	2067*	2022
SMOLAK, K.	STEER, A.	STROMBERG, K.J.
2033*	1530*, 1687*	1709
SMOLER, D.	STEFENELLI, N.	STRONG, E.W.
1706	1552	2138*
SMYK, B.	STEIN, U.	STRYCKMANS, P.A.
1539	2124*	1962
SNART, R.S.	STEINBERG, A.D.	STUART, A.
1648*	1853*	1916

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VENKATESAN, N. 1578	WECHSLER, W. 1588, 1589, 2070*	WOJNAROWSKA, M. 2011
VERMA, D.P.S. 1684*	WEDDERBURN, N. 1801	WOODING, W.L. 1613*
VERMEIL, C. 1818	WEGNER, K. 1550	WOODSIDE, N. 1694
VERNACE, S. 2087*	WEIN, A.J. 1507	WOYKE, S. 2028*, 2157*, 2197*
VERNIER, R.L. 1885	WEISS, B. 1750	YABLONOVSKAYA, L.YA. 1606*
VESSEY, M.P. 1600	WEISS, L. 1969, 1996, 2086*	YAM, L.T. 2091*
VETRAK, J. 1765*	WEISS, M.C. 2056*	YAMAMOTO, T. 1660, 1937*
VILAIN, C. 1701	WEISS, R.A. 1707, 1742	YAMASHITA, J. 2015
VILLANUEVA, N.D. 2024*	WEISS, W. 1942*	YANAGI, S. 1551
VISFLDT, J. 1995	WEISSBACH, A. 1958	YANG, C.-P. 2087*
VIVIAN, A.B. 1959	WELLS, D.G. 1795	YATANI, R. 1676*
VOEIKOV, V.L. 2058*	WENGLER, G. 2189*	YEUNG, D. 1611*
VOGEL, F. 1619*	WERNER, D. 2169*	YIELDING, K.L. 1536
VOGT, P.K. 1707, 1743	WESCOTT, W.B. 1518*	YOSIDA, T.H. 2015
VOLKERS, S.A.S. JJJJQ	WESTERMARK, B. 1952	YOSHIDA, T.O. 2021
VOTRIN, I.I. 2182*	WETTER, O. 2090*	ZABEL-LANGHENNIG, R. 1888
VRANA, M. 1786	WHITFIELD, J.F. 2001	ZAJICEK, J. 2080*
VULKOV, I. 2083*	WICKRAMASINGHE, S.N. 1975	ZALDIVAR, R. 1892
WACHER, A. 2093*	WIECKOWSKA, Z. 1938*	ZALUSKY, R. 1849*
WAHREN, B. 1848*	WIER, K.A. 1668	ZAMCHEK, N. 1839, 1869*
WALFORD, R.L. 1843*	WILBUR, J. 2115*	ZAMECNIK, P.C. 1705
WALLACE, A.C. 1846*	WILBUR, J.R. 1697	ZANJANI, E.D. 1849*
WALLING, M.J. 1694	WILDER, G.P. 1550	ZAVADINA, S.P. 1568
WALSKI, M. 2029*	WILLIAMS, C.E. 1644*	ZEIGEL, R. 2086*
WARREN, L. 1738	WILLIAMS, D.R. 1504	ZELJVIN, B.M. 2156*
WARWICK, G.P. 1514	WILLSON, M.A. 2109*	ZELLER, E. 1843*
WARZOK, R. 1888	WILSON, J.D. 1829	ZELLJADT, I. 1694
WASHINGTON, L.P. 2196*	WINKELSTEIN, A. 2140*	ZIFF, M. 1778*
WATANABE, M. 1983	WISCH, N. 2129*	ZIMMERMAN, D.H. 2048*
WATANABE, T. 1554	WISEMAN, N. 2185*	ZIPPIN, C. 2114*
WATKINS, E., JR. 1864*	WITSCHI, H.P. 1538	ZIPRIN, R. 1858*
WEBSTER, R.G. 1781	WOHLENBERG, C. 1810	ZIPURSKY, A. 1804
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 N-ACETYLAMINOFLUORENE  
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   ANTHRACENE, FETAL RAT (1569)  
   NECROSIS, 7,12-DIMETHYLBENZ(A)-  
   ANTHRACENE, SUPPRESSION, STEROID,  
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   (1546)  
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     (1555)  
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     LIVER REGENERATION, RAT (1557)  
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 AGGLUTINATION  
   COMPLEMENT FIXATION, VIROLOGY (1948)  
 AGING  
   NUCLEIC ACID SYNTHESIS, LIVER, MOUSE  
   (1639)\*  
 AGRICULTURE  
   LEUKEMIA, REVIEW (1520)\*  
 ALDOLASE A  
   HEPATOMA, IMMUNOLOGY, RAT (1949)  
 N-ALKYL-N'-NITRO-N-NITROSOGUANIDINES  
   MUTAGENICITY, HIGHER PLANTS (1642)\*  
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   HISTOPATHOLOGY, KIDNEY, RAT (1542)  
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   LIVER, MALIGNANCY, HUMAN (2144)\*  
   STOMACH CARCINOMA, LIVER METASTASES,  
   HUMAN (1842)\*  
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   LIVER, STRUCTURAL CHANGES, MICRO-  
   CIRCULATION, RAT (1552)  
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   CARCINOMA, HUMAN (2139)\*  
 AMINO ACID  
   UPTAKE, POLYOMA-TRANSFORMED CELL,  
   HAMSTER (1757)  
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   TRANSFORMED CELL, STRAIN LONGEVITY,  
   SV40, HUMAN (1756)  
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   ERYTHROCYTES, RETICULOENDOTHELIAL  
   SYSTEM (1997)  
 ANGIOGENESIS  
   TUMOR, THERAPEUTIC IMPLICATIONS (1895)  
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   ASCITES CELLS, EHRICH, TUMOR (2086)\*  
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   TUMOR PROMOTION, MOUSE (1541)  
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   BIOASSAY, TUMOR CELLS, TETANUS SPONES,  
   HUMAN (2131)\*  
   BLOCKING, SERUM FACTOR, TUMOR HOST  
   (1828)  
   CELL PRODUCTION, PLAQUE-FORMING CELL,  
   IDENTIFICATION (1851)\*  
   EPSTEIN-BARR VIRUS, SERUM, INDONESIA  
   (1833)  
   FORMING CELLS, PROLIFERATION,  
   DIFFERENTIATION, LYMPH, SHEEP  
   (1874)\*  
   HERPESVIRUS, SERUM, SARCOIDOSIS  
   PATIENTS (1848)\*  
   HL-A ANTIBODY, ANTILYMPHOCYTE SERUM,  
   HUMAN (1871)\*  
   LYMPHOCYTE, PROSTATE CARCINOMA, HUMAN  
   (1865)\*  
   PRODUCTION, BENZO(A)PYRENE, TUMOR  
   INCIDENCE, MOUSE (1573)  
   RNA, IMMUNOGENICITY MECHANISM,  
   IMMUNOLOGICAL TEMPLATE (1858)\*  
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   FIBRINOLYSIS, (1521)\*  
 ANTIGEN  
   ABH ISOANTIGENS, EPITHELIAL, PRIMARY  
   STOMACH TUMOR, METASTASES, HUMAN  
   (1839)



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 CARCINOEMBRYONIC ANTIGEN, DIGESTIVE  
 TRACT CARCINOMA, HUMAN (1869)\*  
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   GASTROINTESTINAL TUMOR,  
   X-RAY, RODENT (1659)  
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   COLON TUMOR-SPECIFIC, HUMAN (1827)  
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   GROUP-SPECIFIC, AVIAN SARCOMA-  
   LEUKOSIS VIRUS, ROUS SARCOMA VIRUS  
   INDUCED TUMOR, HAMSTER, CHICK (1792)  
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   MODULATION, MOUSE (1845)\*  
   IGA, IMMUNE RESPONSE, GENETIC  
   CONTROL, MOUSE (1813)  
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   ANTILYMPHOCYTE SERUM, ANTIBODY,  
   HUMAN (1871)\*  
   HODGKIN'S DISEASE, GROUP FIVE  
   SYSTEM, HUMAN (1789)  
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   PATIENTS' FAMILIES (1825)  
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   HUMAN (1844)\*  
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 HEPATITIS-ASSOCIATED  
   IMMUNOLOGY (1953)  
   LIVER CELL CARCINOMA,  
   TAIWAN (1797)  
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   BIOCHEMISTRY (1847)\*  
   CELL ACTIVATION, THYMUS, MOUSE  
   (1860)\*  
   GENE, PARENTAL VARIANT (1821)  
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 (1837)  
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 RAT (1832)  
 NUCLEAR, HUMAN, CHICK, CHICK ERYTHRO-  
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 VARICELLA HERPES ZOSTER (1775)\*  
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   LEUKEMIC CELL, MURINE LEUKEMIA  
   VIRUS, MOUSE (1814)  
   VIRUS RELEASE, FIBROBLAST,  
   MOLONEY LYMPHOMA CELL, HYBRID,  
   MOUSE (1784)  
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   SYNTHESIS, DEGRADATION, POLYOMA  
   VIRUS, MOUSE (1836)  
   TRANSIENT IMMUNE RESPONSE, HUMAN  
   (1794)  
   TUMOR CELL, YOSHIDA ASCITES HEPATOMA,  
   CELL ELECTROPHORESIS (1822)  
   TUMOR CELL A-LIKE, PROTEASE,  
   RESISTANCE, HELIX POMATIA (1863)\*  
   TUMOR-SPECIFIC, NORMAL CELL, VIRAL  
   CARCINOGENESIS, MOUSE (1877)\*  
   TYPE-SPECIFIC SURFACE, HERPES SIMPLEX  
   VIRUS, INFECTED CELL, HUMAN (1719)  
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   HL-A ANTIGEN, ANTIBODY, HUMAN (1871)\*  
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   LYMPHOID MEMBRANE COMPONENT, IMMUNE  
   REACTIVITY, HUMAN (1819)  
   TUMOR METASTASIS, 9,10-DIMETHYLBENZ-  
   1,2-BENZANTHRACENE, RAT (1876)\*  
 ARGININE  
   REQUIREMENT, MECHANISM, ADENOVIRUS  
   SYNTHESIS (1713)  
 AROMATIC NITROGEN MUSTARD  
   DERIVATIVES, MACROMOLECULE,  
   HYDROLYSIS (1625)\*  
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   EHRlich, TUMOR, ANIONIC SITES (2086)\*  
   54MN UPTAKE (2075)\*  
   POLYADENYLIC ACID, MRNA, MOUSE (1974)  
   SUSPENSION, ION PERMEABILITY, MICE  
   (2058)\*

- TUMOR, 67 GALLIUM, MICE (2082)\*
- ASCITES TUMOR  
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- ASCITES TUMOR CELL  
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- L-ASPARAGINE  
IN VITRO, LEUKEMIC CELLS (2190)\*
- ASTROCYTE  
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- ATOMIC BOMB  
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LEUKEMIA (1663)  
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STOMACH CANCER, JAPAN (1937)\*
- ATP-SULFURYLASE  
MASTOCYTOMA, PROPERTIES, MOUSE (2085)\*
- AUDITORY MEATUS  
TUMOR, ORGANOTROPY,  
N-2-FLUORENYLACETAMIDE, RAT (1553)
- AUSTRALIAN ANTIGEN  
LEUKEMIA, LYMPHATIC, PERIARTERITIS NODOSA, HUMAN (2087)\*
- AUTOIMMUNITY  
SKIN, CHANGES, CARCINOMA (1856)\*  
THYROIDITIS, METHYLCHOLANTHRENE, RAT (1815)
- AUTORADIOGRAPHY  
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- AUTOSOMES  
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- BACILLUS CALMETTE-GUERIN  
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- BACTERIOPHAGE  
F2, RNA, INTERFERON INDUCTION (1765)\*  
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- BASAL CELL  
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EFFECTS, MAMMARY TUMOR, RAT (1990)
- BENIGN  
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- BENIGN LESION  
ATYPICAL CHARACTERISTIC, CANCER RISK, HUMAN (1881)
- BENZO(A)PYRENE  
CARCINOGENICITY, IODINE, MOUSE (1577)  
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METABOLISM, HAMSTER EMBRYO CELLS, IN VITRO (1568)  
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FURFURAL, RESPIRATORY TRACT TUMOR, HAMSTER (1574)  
LIVER, MICROSOMAL MIXED-FUNCTION OXIDASE, RAT, MOUSE (1650)\*  
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TUMOR INCIDENCE, ANTIBODY PRODUCTION, MOUSE (1573)
- 2-BETA-AMINOETHYLISOTHIOURONIUM  
X-RAY, CANCER, RAT (1674)\*
- BETA-DIETHYLAMINOETHYL DIPHENYLPROPYL-ACETATE  
LIVER MICROSOMAL AZOREDUCTASE, PHENOBARBITAL, 3-METHYLCHOLANTHRENE, RAT (1627)\*
- BILE  
FLOW RATE, SODIUM PHENOBARBITOL, DIMETHYLNITROSAMINE, RAT (1614)\*
- BIOPSY  
TUMOR SPREAD, HUMAN (2080)\*
- BLADDER  
CARCINOMA  
BILHARZIAL, PREGNANCY, LABOR, HUMAN (1979)  
CYCLAMATE, DIABETES MELLITUS



(1636)\*  
BLAST CELLS  
MATURATION, AUTORADIOGRAPHY,  
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MOUSE (2098)\*  
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TRANSPLACENTAL  
DIMETHYLNITROSAMINE,  
NITROSOMETHYLUREA, MOUSE (1607)\*  
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DIMETHYLNITROSAMINE, MOUSE  
(1603)\*  
BLOCKING FACTOR  
TRANSPLANTATION IMMUNITY, REVIEW  
(1509)  
BLOOD  
CHANGES  
7,12-DIMETHYLBENZ(A)ANTHRACENE,  
SPIRONOLACTONE, PROADIFEN, RAT  
(1571)  
RADIO IODINE THERAPY, HUMAN (1666)  
CHRONIC MYELOID LEUKEMIA, SERUM,  
VITAMIN B12 BINDING, HUMAN (1960)  
DISEASE, ONCOGENESIS, MYCOTOXIN (1539)  
LYMPHOCYTE, CHRONIC LYMPHOCYTIC  
LEUKEMIA, SURFACE IMMUNOGLOBULIN,  
HUMAN (1829)  
LYMPHOCYTE COUNT, X-RAY, RAT (1672)\*  
MALIGNANT DISEASE, HL-A ANTIGEN  
FREQUENCY, HUMAN (1807)  
BLOOD GROUP  
GASTRIC CANCER, AGE, SEX, INCIDENCE,  
LONDON (1924)  
BONE  
NEOPLASM, METASTASES, SCAN, HUMAN  
(2071)\*  
SARCOMA  
EWING'S ULTRASTRUCTURE (2179)\*  
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CHANGES, RADIO IODINE THERAPY, HUMAN  
(1666)  
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HAMSTER (1654)\*  
GAMMA-RAY, GUINEA PIGS (1671)\*  
ILMAPOIETIC CELLS, INHIBITION,  
NEOPLASM, MOUSE (2077)\*  
LEUKEMIA, ELECTRON MICROSCOPE, RAT  
(1969)  
LYMPHOCYTE COUNT, X-RAY, RAT (1672)\*  
SERUM COPPER, HUMAN (2115)\*  
BRAIN  
CEREBELLUM, PRECANCEROUS CHANGE,  
9,10-DIMETHYL-1,2-BENZANTHRACENE  
(1606)\*  
MEDULLOBLASTOMA, RNA-DEPENDENT DNA  
POLYMERASE, HUMAN (1984)  
TUMOR  
EXPERIMENTAL INDUCTION, HISTO-  
GENESIS, RAT (1888)  
N-METHYL-N-NITROSOURA, RAT (1592)  
ULTRASTRUCTURE, N-METHYL-N-NITROSOURA  
RAT (1638)\*  
BREAST  
CANCER  
ESTROGEN RECEPTORS, HUMAN (2159)\*  
INCIDENCE, MORTALITY, NORTH  
AMERICA (1920)  
CANCER RISK, BENIGN LESION, ATYPICAL  
CHARACTERISTICS, HUMAN (1881)  
CARCINOMA  
INTRA-EPITHELIAL, ULTRASTRUCTURE,  
HUMAN (2099)\*  
MORTALITY  
UNITED STATES (1944)\*  
YUGOSLAVIA (1926)  
5-BROMODEOXYURIDINE  
FOCUS FORMING VIRUS, GENOME RESCUE,  
NON-PRODUCTIVE CELL, RAT (1731)  
BRONCHIAL  
CANCER, HUMAN (2112)\*  
BURKITT'S LYMPHOMA  
CELLS, OCULAR HERPES SIMPLEX VIRUS,  
INFECTION INHIBITION, HUMAN (1725)  
BURN  
NUCLEIC ACID SYNTHESIS, REVERSIBLE  
ALTERATION, HUMAN (1683)\*  
CAFFEINE  
NUCLEIC ACID SYNTHESIS, LIVER, MOUSE  
(1639)\*  
CANCER  
BASAL CELL, SCAR TISSUE, HUMAN (2196)\*  
BREAST, STROMA, ULTRASTRUCTURE, HUMAN  
(2033)\*  
BRONCHIAL, HUMAN (2112)\*  
GASTRIC  
HISTOLOGY, PROGNOSIS, HUMAN  
(2105)\*  
SEROLOGICAL REACTION, HUMAN  
(2104)\*  
INCIDENCE  
CONNECTICUT (1947)\*  
THAILAND (1931)  
MORTALITY, INDIA (1930)  
PREINVASIVE, ULTRASTRUCTURE, CORNEAL  
EPITHELIUM (1886)  
STOMACH, SURGERY, BENIGN, HUMAN  
(2188)\*

CANCEROGENESIS  
   INVERTEBRATES, EXPERIMENTAL ANIMAL,  
   SNAIL (1956)  
 CARCINOGENICITY  
   CYTOSTATIC SUBSTANCE, REVIEW (1513)  
   SOOT, BENZO(A)PYRENE, MOUSE (1602)  
 CARCINOMA  
   ALVEOLAR CELL, HUMAN (2139)\*  
   AUTOIMMUNOLOGICAL CHANGES, SKIN  
   (1856)\*  
   BASAL CELL  
     ELECTRON MICROSCOPY, HUMAN (2079)\*  
     TRAUMA INDUCED, HUMAN (2100)\*  
   BLADDER, BILHARZIAL, PREGNANCY, LABOR,  
   HUMAN (1979)  
   BREAST  
     INTRA-EPITHELIAL, ULTRASTRUCTURE,  
     HUMAN (2099)\*  
     METASTASES, ESOPHAGUS, HUMAN  
     (2133)\*  
   COLON, IMMUNE REACTIVITY, HUMAN  
   (1808)\*  
   COMPLICATION, ILEOCYSTOPLASTY, HUMAN  
   (2057)\*  
   DIGESTIVE TRACT, CARCINOEMBRYONIC  
   ANTIGEN, HUMAN (1809)\*  
   EHRlich, TRANSPLANT, MICE (2051)\*  
   EHRlich ASCITES, LIVER, LIPIDS, MOUSE  
   (2088)\*  
   EPIDERMAL, MITOTIC INHIBITION, MICE  
   (2073)\*  
   GASTRIC  
     HUMAN (2026)\*  
     IMMUNOLOGIC DISORDERS, HUMAN  
     (2024)\*  
   HYPOPHARYNGEAL, HUMAN CELL LINE  
   (2117)\*  
   ISLET CELLS, STAINING TECHNIQUES,  
   HUMAN (2199)\*  
   LOCALIZATION, PROSTATIC (1526)\*  
   LUNG, OCCUPATIONAL HAZARD, INCIDENCE,  
   SWEDEN (1928)  
   MAMMARY  
     ESTRADIOL RECEPTORS (2007)  
     METASTASES, AXILLARY NODES, HUMAN  
     (2114)\*  
   MICROINVASIVE SQUAMOUS CELL, UTERINE  
   CERVIX, HUMAN (1887)  
   OVARY  
     CHROMATIN BODIES, HUMAN (2065)\*  
     ENDOMETRIOD, METASTASES (1967)  
   PAROTID GLAND  
     ACINIC CELL  
     ULTRASTRUCTURE  
     HUMAN (2106)\*, (2135)\*  
   PRIMARY, LIVER, GLUTAMIC DEHYDRO-  
   GENASE (2102)\*  
   PROSTATE, ARGENTAFFIN CELLS,  
   DIFFERENTIATION, LIPO FUSCIN,  
   MELANIN, PROSTATIC EPITHELIUM (1883)  
   RENAL, FAMILIAL, HUMAN (2166)\*  
   SKIN, IMMUNE RESPONSL, HUMAN (1867)\*  
   SQUAMOUS CERVIX, HOST RESPONSE,  
   CELLULAR IMMUNITY, HUMAN (1820)  
   THYROID  
     DIAGNOSIS, THERAPY, HUMAN (2050)\*  
     HUMAN (2084)\*, (2145)\*  
   WALKER 256, GROWTH, SEROMUCOID  
   FRACTION, OXYPHENBUTAZONE, RAT  
   (1626)\*  
 CARCINOSARCOMA  
   BLADDER, HUMAN (2180)\*  
   TRANSPLANTABLE, GROWTH PROMOTION,  
   CREATININE, MOUSE (1629)\*  
 CATECHOLAMINE  
   CELLS, CULTURE (2171)\*  
   GLIAL CELLS, CULTURE, RAT (2164)\*  
 CELIAC DISEASE  
   LYMPHOCYTE REACTIVITY, IMPAIRMENT,  
   HUMAN (1835)  
 CELL  
   ANTIBODY-PRODUCING, PLAQUE-FORMING  
   CELL, IDENTIFICATION (1651)\*  
   ARGENTAFFIN, PROSTATE CARCINOMA,  
   DIFFERENTIATION, LIPO FUSCIN,  
   MELANIN, PROSTATIC EPITHELIUM (1883)  
   ASCITES, SUSPENSION, ION PERMEABILITY,  
   MICE (2058)\*  
   CULTURE  
     CATECHOLAMINES (2171)\*  
     CHEMICAL RESPONSE, GLUCAGON,  
     EPINEPHRINE, PROSTOGLANDINS  
     (2103)\*  
   EARLY PROLIFERATION, HEMOPOIESIS,  
   ULTRASTRUCTURE, MOUSE (1903)\*  
   LEUKEMIC, SURFACE ANTIGEN, MURINE  
   LEUKEMIA VIRUS, MOUSE (1814)  
   LYMPH NODE, GAMMAGLOBULIN, SYNTHESIS,  
   SECRETION (2048)\*  
   MALIGNANT GLIAL, ADENYL CYCLASE,  
   PHOSPHODIESTERASE, CYCLIC AMP  
   DEPENDENT PROTEIN KINASE (1904)\*  
   MEMBRANE, ALLOANTIGENS,  
   LYMPHOID LOCI, REVIEW (1516)  
   MURINE TUMOR, SYNTHESIS, L-ASPARAGINE  
   (2047)\*  
   NONPRODUCTIVE  
     EPSTEIN-BARR VIRUS, GENOME  
     DETECTION (1703)  
     FOCUS FORMING VIRUS, GENOME



RESCUE, 5'-BROMODEOXYURIDINE, RAT (1731)  
 MURINE SARCOMA VIRUS, GENOME RESCUE KINETICS, MOUSE (1735)  
 OPSONIC ADHERENCE, VENERAL TUMOR, DOG (1878)\*  
 PROLIFERATION  
   GENE ACTIVATION, PROTEIN SYNTHESIS REQUIREMENT, HUMAN FIBROBLAST (1884)  
   NORMAL TISSUE, MALIGNANT TISSUE, REVIEW (1503)  
   SEBACEOUS GLAND, LABELLING INDEX, REGIONAL VARIATIONS, HUMAN (1880)  
 TRANSFORMED  
   CONCANAVALIN A BINDING, IMMUNO-FLUORESCENCE, MOUSE (1830)  
   MURINE SARCOMA VIRUS PRODUCTION, CLONAL ISOLATION, RAT (1729)  
   RNA TUMOR VIRUS, GLYCOSIDASE, PROTEOLYTIC ENZYME, MOUSE (1741)  
 TUMOR  
   ASCITES, 67 GALLIUM, MICE (2082)\*  
   MEMBRANES, TOPOLOGY (2009)  
   VOLUME, CIGARETTE SMOKING, HUMAN (1637)\*  
 L-CELL  
   MACROPHAGE HYBRID, IMMUNOLOGIC PROPERTIES (1850)\*  
 CELL CYCLE  
   CARCINOGENESIS, REVIEW (1514)  
   PHASE PROGRESSION, LEUKEMIC CELL, ACTINOMYCIN D, PUROMYCIN, MOUSE (1630)\*  
 CELL MEMBRANE  
   TUMORIGENESIS, CONCANAVALIN A, HUMAN (2093)\*  
 CELL PROLIFERATION  
   THYMUS, STIMULATION, RAT (2001)  
 CELL SURFACE ANTIGEN  
   MALIGNANT DISEASE, REVIEW (1510)  
 CEREBRAL  
   GLIOMAS, ULTRASTRUCTURE, HUMAN (2070)\*  
 CERVIX  
   ADENOCARCINOMA, MESONEPHRIC, HUMAN (2111)\*  
   CARCINOMA, HERPESVIRUS TYPE 2, SEROEPIDEMIOLOGIC STUDY (1718)  
   PERITONEAL, METASTASIS, REVIEW (1524)\*  
   SQUAMOUS CARCINOMA, HOST RESPONSE, CELLULAR IMMUNITY, HUMAN (1820)  
   TUMOR, HERPESVIRUS TYPE 2, ISOLATION, HUMAN (1723)  
 CERVIX UTERI  
   CARCINOMA, MORTALITY, INTERNATIONAL (1921)  
   MALIGNANCY, HISTOLOGY, DNA, HUMAN (2089)\*  
 CHEMICAL CARCINOGEN  
   AVIAN TUMOR VIRUS INDUCTION, NORMAL CHICK CELL (1707)  
   TRANSFORMATION IN VITRO, HAMSTER EMBRYO CELL (1591)  
   TRANSPLACENTAL, HUMAN, REVIEW (1505)  
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   IMMUNITY, MUTATION, NEOPLASM, REVIEW (1522)\*  
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   HEPATOMA, FEEDBACK, RAT (1968)  
   LIPID ANOMALY, LIVER, AFLATOXIN, DUCKLING (1622)\*  
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   ASCITES TUMOR CELLS, RESISTANCE, DAUNORUBICINE (1995)  
   HARDING-PASSEY MELANOMA, KIDNEY TUMOR (2030)\*  
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   LEUKEMIA, (1525)\*  
   LEUKEMOGENIC RESPONSE, RADIATION, MOUSE (1665)  
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   NASOPHARYNGEAL CANCER, HUMAN (2021)  
   PLOIDY FLUCTUATIONS, PLASMA CELL TUMOR, TRANSPLANTATION, MOUSE (2015)  
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   NUCLEIC ACID, SMALL MOLECULES,

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- DIET  
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   NEUROHISTOLOGY, EVOLUTIONARY ASPECTS (1897)\*  
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   LIVER, MICROSOMAL METABOLITES, POLYCYCLIC HYDROCARBONS, RAT (1533)  
   PLASMA (2000)  
   SERUM INHIBITOR LOSS, THYMOMA, ERYTHROCYTE APLASIA, CASE REPORT (1849)\*  
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   ANEMIA, RETICULOENDOTHELIAL SYSTEM (1997)  
   APLASIA, THYMOMA, ERYTHROPOIESIS, SERUM INHIBITOR LOSS, CASE REPORT (1849)\*  
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   ERYTHROBLASTOSIS, PROLIFERATION (1910)\*  
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   CARCINOMA  
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     NITROSAMINE, DISTILLED SPIRITS, EAST AFRICA (1583)  
   CHEMICAL BURN SCAR, TRANSFORMATION, CASE REPORT (1609)\*  
   TUMOR, N-METHYLBENZYLAMINE, SODIUM NITRITE, RAT (1608)\*  
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   ESTRADIOL, TUMORS (1959)  
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   LIVER CARCINOGENESIS, LITHOCHOLIC ACID, RAT (1554)  
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   CORNEAL EPITHELIUM, PREINVASIVE CANCER, ULTRASTRUCTURE (1886)  
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   CASE REPORT (1939)\*  
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   METABOLISM, GROWTH HORMONE, RAT

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   METASTASIS, STOMACH CARCINOMA, ALPHA FETOPROTEIN, HUMAN (1842)\*  
   3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, PYRUVATE KINASE ISOZYME, RAT (1562)  
   MICROSOMAL AZOREDUCTASE, BETA-DIETHYL-AMINOETHYL DIPHENYLPROPYLACETATE, 2,4-DICHLORO-6-PHENOXYETHYLAMINE, PHENOBARBITAL, 3-METHYLCHOLANTHRENE, RAT (1627)\*  
   MICROSOMAL MIXED-FUNCTION OXIDASE, BENZO(A)PYRENE, RAT, MOUSE (1650)\*  
   NUCLEIC ACID SYNTHESIS  
     AGING, CAFFEINE, RADIATION, MOUSE (1639)\*  
     DIMETHYLNITROSAMINE, RAT (1587)

PARENCHYMA, INJURY, AFLATOXIN B1,  
 ULTRASTRUCTURE, RAT (1635)\*  
 POLYSOMAL DISAGGREGATION, DIMETHYL-  
 NITROSAMINE, LASIOCARPINE,  
 2-DIETHYLAMINOETHYL-2,2-DIPHENYL-  
 VALERATE, MOUSE (1652)\*  
 PROTEIN LABELING, DIMETHYLNITROSAMINE,  
 3-METHYLCHOLANTHRENE PRETREATMENT,  
 RAT (1586)  
 REGENERATION  
 AFLATOXIN, RAT (1557)  
 DIETHYLNITROSAMINE, HEPATECTOMY,  
 RAT (1633)\*  
 SERUM PROTEIN, SOLUBLE PROTEIN,  
 ELECTROPHORETIC ANALYSIS, HEPATO-  
 CARCINOGENESIS, MOUSE (1893)  
 STRUCTURAL CHANGES, MICROCIRCULATION,  
 ALPHA-NAPHTHYL-ISOTHIOCYANATE, RAT  
 (1552)  
 TUMOR  
 ENDOPLASMIC RETICULUM, LIPID,  
 GLYCOGEN, RAT (1986)  
 ISOZYME, N,N'-2,7-FLUORENYLENE-  
 BISACETAMIDE, MOUSE (1551)  
 YOSHIDA ASCITES HEPATOMA, TUMOR CELL  
 ANTIGEN, CELL ELECTROPHORESIS (1822)  
 LIVER CELLS  
 TRANSPLANTATION, HISTOLOGY, RAT  
 (2034)\*  
 LIVER NEOPLASMS  
 VIRAL HEPATITIS, METASTASIS, REVIEW  
 (1528)\*  
 LOCALIZATION  
 CARCINOMA, PROSTATIC (1526)\*  
 LONGEVITY  
 TRANSFORMED AMNION CELL, SV40, HUMAN  
 (1756)  
 LUNG  
 BRONCHIAL ADENOMA, METHYLNITROSOUREA,  
 ORGANOTROPISM, MOUSE (1590)  
 CANCER, RISK FACTORS, AGE (1942)\*  
 CARCINOMA  
 CIGARETTE SMOKING HUMAN (1617)\*  
 INCIDENCE  
 AGE FACTOR, RUSSIA (1946)\*  
 STATISTICAL PROCEDURE (1940)\*  
 PNEUMOSCLEROSIS, HUMAN (1899)\*  
 RADON IRRADIATION, OCCUPATIONAL  
 HAZARD (1691)\*  
 DISEASE, DELAYED HYPERSENSITIVITY  
 (1861)\*  
 EFFUSION, RNA VIRUS PARTICLE, HUMAN  
 (1692)  
 MESOTHELIOMA, DIAGNOSIS, AUTOPSY  
 (1934)\*  
 TUMOR  
 ACINIC CELL, HUMAN (2165)\*  
 BENZO(A)PYRENE, 1,2,5,6-DIBENZ-  
 ANTHRACENE, 7,12-DIMETHYLBENZ(A)  
 ANTHRACENE, DOSE RESPONSE RAT  
 (1576)  
 LYMPH NODE  
 ANTITUMOR ACTIVITY, SARCOMA, METHYL-  
 CHOLANTHRENE, MOUSE (1826)  
 CELLS, GAMMA GLOBULIN, SYNTHESIS,  
 SECRETION (2048)\*  
 IMMUNOLOGIC COMPETENCE, MAMMARY  
 CARCINOMA, HUMAN (1788)  
 IRRADIATION, BARRIER, RABBIT (2061)\*  
 LYMPHOCYTE  
 ACTIVITY, NEOPLASMA, HUMAN (2126)\*  
 ANTIBODY, PROSTATE CARCINOMA, HUMAN  
 (1865)\*  
 ANTIGEN BINDING, SPECIFICITY (1837)  
 BLASTIC TRANSFORMATION  
 INHIBITION, ANTI-HL-A SERUM, HUMAN  
 (1879)\*  
 RETICULO ENDOTHELIAL MALIGNANCY,  
 HUMAN (1862)\*  
 BLOOD, CHRONIC LYMPHOCYTIC LEUKEMIA,  
 SURFACE IMMUNOGLOBULIN, HUMAN (1829)  
 INHIBITION, LYMPHOSARCOMA CELLS,  
 HUMAN (1800)  
 IN-VITRO ACTIVATION, HUMAN (2031)\*  
 LEUKEMIA, HISTOLOGY (2045)\*  
 LONG-LIVED, RECOVERY, RADIATION, RAT  
 (1679)\*  
 MOLONEY VIRUS-TRANSFORMED, IMMUNE  
 LYSIS, CELL CYCLE-DEPENDENT, VIRAL  
 ANTIGEN, RAT (1832)  
 RADIATION EFFECT, HUMAN (1677)\*  
 REACTIVITY IMPAIRMENT, CELIAC DISEASE,  
 HUMAN (1835)  
 T AND B, CHRONIC LYMPHOCYTIC LEUKEMIA,  
 HUMAN (1855)\*  
 TRANSFORMATION, ACUTE LYMPHOBLASTIC  
 LEUKEMIA, HUMAN (1795)  
 LYMPHOCYTIC LEUKEMIA  
 PATHOGENESIS, GASTRIC CARCINOMA  
 (1907)\*  
 LYMPHOGANULOMATOSIS  
 IMMUNOLOGICAL DETERMINATION, HUMAN  
 (1857)\*  
 LYMPHOID CELLS  
 LEUKEMIA, ELECTRON MICROSCOPY, HUMAN  
 (2078)\*  
 LYMPHOMA  
 BURKITT'S, CLINICAL ASPECTS (2049)\*  
 CHEMICALLY MODIFIED CELL, IMMUNIZATION  
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MALIGNANT, RHESUS MONKEY (2040)\*  
 VIRAL INDUCTION, GRAFT-VERSUS-HOST  
 REACTION, MOUSE (1780)  
 LYMPHORETICULOSARCOMA  
 IMMUNOLOGICAL DETERMINATION, HUMAN  
 (1857)\*  
 LYMPHOSARCOMA  
 BINDING, DIBENZ(A,H)ANTHRACENE,  
 DIBENZ(A,C)ANTHRACENE, MOUSE EMBRYO  
 CELL (1565)  
 LYSOSOME  
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 (2120)\*  
 LIVER, AFLATOXIN, RAT (1621)\*  
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 LEUKEMIA, ACUTE, CHRONIC (2017)  
 MACROMOLECULE  
 AROMATIC NITROGEN MUSTARD DERIVATIVES,  
 HYDROLYSIS (1625)\*  
 MACROPHAGE  
 L-CELL HYBRID, IMMUNOLOGIC PROPERTIES  
 (1850)\*  
 MALIGNANCY  
 CERVIX UTERI, HISTOLOGY, DNA, HUMAN  
 (2089)\*  
 CHORION (1987)  
 LIVER, ALPHA-FETOPROTEIN, HUMAN  
 (2144)\*  
 MALIGNANCY ASSOCIATED CHANGES  
 NUCLEAR ABERRATION, CLASSIFICATION,  
 HUMAN (1891)  
 MALIGNANT  
 ENDOCRINE, ADRENAL, EVOLUTION, HUMAN  
 (1978)  
 LYMPHOMA, RHESUS MONKEY (2040)\*  
 MALIGNANT CHANGE  
 WOUND, SCAR, HUMAN, REVIEW (1507)  
 MALIGNANT DISEASE  
 CORONARY HEART DISEASE, RELATIONSHIP  
 (1915)  
 MALIGNANT LYMPHOMA  
 ATOMIC BOMB SURVIVOR, INCIDENCE, JAPAN  
 (1656)  
 MALIGNANT TISSUE  
 NORMAL TISSUE, CELL PROLIFERATION,  
 REVIEW (1503)  
 MAMMARY CARCINOMA  
 ESTRADIOL RECEPTORS (2007)  
 METASTASES (2036)\*  
 AXILLARY NODES, HUMAN (2114)\*  
 PROTECTION, HORMONE, HUMAN (1616)\*  
 MAMMARY GLAND  
 CARCINOMA  
 ANTIGENIC CHANGES, HUMAN (1786)  
 GROWTH, 7,12-DIMETHYLBENZ(A)ANTH-  
 RACENE, INSULIN, OOPHORECTOMY,  
 HYPOPHYSECTOMY, RAT (1563)  
 LYMPH NODE IMMUNOCOMPETENCE, HUMAN  
 (1788)  
 METASTASIS (2119)\*  
 ONCOGENIC RNA VIRUS, MONKEY,  
 (1694)  
 ORAL CONTRACEPTIVE (1600)  
 SERUM IMMUNOFLOUORESCENCE, HUMAN  
 (1802)  
 VIRUS, NUCLEIC ACID, DNA POLYMER-  
 ASE, MONKEY (1696)  
 VIRUS PARTICLE PENETRATION,  
 PRODUCTIVE CELL, MOUSE (1701)  
 CARCINOMA IN SITU, INFILTRATIVE  
 CARCINOMA, PATHOGENESIS, REVIEW  
 (1515)  
 MILK, VIRUS-LIKE PARTICLE, HUMAN  
 (1693)  
 PARENCHYMA DNA, 7,12-DIMETHYLBENZ(A)-  
 ANTHRACENE, BINDING, RAT (1564)  
 TUMOR  
 7,12-DIMETHYLBENZ(A)ANTHRACENE,  
 PROGESTERONE, OVARIECTOMY,  
 ADRENALECTOMY, RAT (1546)  
 MASON-PFIZER VIRUS, SEROLOGY,  
 STRUCTURE, MONKEY (1695)  
 RNA VIRUS PARTICLE, HUMAN (1692)  
 TUMOR EXTRACT, DELAYED HYPER-  
 SENSITIVITY, SURVIVAL, HUMAN (1641)\*  
 TUMOR VIRUS, HUMAN, REVIEW (1501)  
 MAMMARY TUMORS  
 REGRESSION, ERGOT DRUGS, RAT (1951)  
 VASCULAR SUPPLY, MOUSE (2003)  
 MANNOSAMINE  
 ASCITES TUMOR CELL, ULTRASTRUCTURE,  
 RAT (1534)  
 MAST CELL  
 NEOPLASMS, CAT (1992)  
 MASTOCYTOMA  
 ATP-SULFURYLASE, PROPERTIES, MOUSE  
 (2085)\*  
 CELL IMMUNIZATION, CYTOLYTIC LYMPHOID  
 CELL, INDUCTION, MOUSE (1811)  
 DEGRADATION, HEPARIN, MOUSE (2163)\*  
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 (2020)  
 METABOLISM, MOUSE (2178)\*  
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- CYTOCHEMISTRY, KARYOMETRICS, HUMAN (2062)\*  
 ETIOLOGY, COMMUNICABLE (1519)\*  
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 JUVENILES, HUMAN (2038)\*  
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 PROPERTIES, MICE (2055)\*
- MENINGIOMA  
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 FIBROBLASTIC, HUMAN (2157)\*  
 HEMANGIOBLASTOMA, ELECTRON MICROSCOPY, HUMAN (2081)\*
- MESOTHELIOMA  
 LUNG, DIAGNOSIS, AUTOPSY (1934)\*  
 ULTRASTRUCTURE, ADENOMATOID, HUMAN (2110)\*
- METABOLISM  
 AFLATOXINS, RAT (1640)\*  
 BENZO(A)PYRENE,  
 7,12-DIMETHYLBENZ(A)ANTHRACENE,  
 HAMSTER EMBRYO CELLS, IN VITRO (1568)  
 DIBENZ(A,H)ANTHRACENE, DIBENZ(A,C)-  
 ANTHRACENE, MOUSE EMBRYO CELL (1565)  
 7,12-DIMETHYLBENZ(A)ANTHRACENE,  
 3-METHYLCHOLANTHRENE PRETREATMENT,  
 DIGESTIVE TRACT, RAT (1570)  
 ENZYMES, LEUKOCYTE, REVIEW (1517)  
 HISTAMINE, PRETUMOROUS GASTRIC  
 DISEASES, HUMAN (1901)\*  
 LIVER, POLYCYCLIC HYDROCARBONS,  
 EPOXIDES, RAT (1533)
- METAL  
 LIGAND, CARCINOGENESIS, REVIEW (1504)
- METASTASIS  
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 AXILLARY NODES, MAMMARY, CARCINOMA,  
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 BASALIOMA, CONNECTIVE TISSUE (2184)\*  
 CARCINOMA, OVARY, ENDOMETRIOD (1967)  
 CRYPTOGENIC, INCIDENCE, UGANDA (1918)  
 ESOPHAGUS, CARCINOMA, BREAST, HUMAN  
 (2133)\*  
 HEPATIC, REGRESSION, HUMAN (2162)\*  
 LIVER NEOPLASMS, VIRAL HEPATITIS,  
 REVIEW (1528)\*  
 MALIGNANT NEAVI, BONE, HUMAN (2053)\*  
 MAMMARY CARCINOMA (2036)\*, (2119)\*  
 NECK, HUMAN (2160)\*  
 NEOPLASM, BONE, SCAN, HUMAN (2071)\*  
 ORGAN DISTRIBUTION, INCIDENCE, HAMSTER  
 (2192)\*  
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 PERITONEAL, CERVIX, REVIEW (1524)\*
- RETICULUM CELL, SARCOMA, TRANSPLANT,  
 HUMAN (2113)\*  
 SARCOMA, RETICULUM CELL, SPLEEN, MICE  
 (1981)  
 SKIN, PRIMARY, GASTROINTESTINAL,  
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 TUMOR, OXYGEN, MICE (2185)\*
- METHYL METHANE SULFONATE  
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 SINGLE STRAND DNA BREAKS, NITROSO-  
 GUANIDINE, HAEMOPHILUS INFLUENZAE  
 (1540)
- N-METHYLBENZYLAMINE  
 SODIUM NITRITE, ESOPHAGEAL TUMOR, RAT  
 (1608)\*
- METHYLCHOLANTHRENE  
 ENDOMETRIAL CARCINOMA, ULTRASTRUCTURE,  
 HISTOLOGY, MOUSE, RAT (1632)\*  
 SARCOMA, ANTITUMOR ACTIVITY, LYMPH  
 NODES, MOUSE (1826)  
 THYROIDITIS, AUTOIMMUNITY, RAT (1815)
- 3-METHYLCHOLANTHRENE  
 DERIVATIVES, BENZO(A)PYRENE  
 HYDROXYLASE, LIVER, FETAL RAT (1580)  
 ENDOPLASMIC RETICULUM, PROTEIN, RAT  
 (1579)  
 KIDNEY CELL, TRANSFORMATION, MOUSE  
 (1582)  
 LIVER, ENDOPLASMIC RETICULUM,  
 PROLIFERATION, ULTRASTRUCTURE, RAT  
 (1655)\*  
 LIVER MICROSOMAL AZOREDUCTASE,  
 2,4-DICHLORO-6-PHENOXYETHYLAMINE,  
 BETA-DIETHYLAMINOETHYL DIPHENYL-  
 PROPYLACETATE, RAT (1627)\*  
 PRETREATMENT, 7,12-DIMETHYLBENZ(A)-  
 ANTHRACENE, METABOLISM, DIGESTIVE  
 TRACT, RAT (1570)  
 SARCOMA GROWTH, PREDNISONE (1604)\*  
 TUMOR, C-TYPE RNA VIRUS, ISOLATION,  
 HAMSTER (1581)
- 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE  
 DIET, LEUCINE INCORPORATION, RAT  
 (1559)
- LIVER  
 DNA SYNTHESIS, RAT (1560)  
 PYRUVATE KINASE ISOZYME, RAT  
 (1562)
- 3-METHYL-4-NITROPYRIDINE-1-OXIDE  
 FIBROSARCOMA, MOUSE (1593)
- N-METHYL-N-NITROSOUREA  
 BRAIN TUMOR, SPINAL TUMOR, RAT (1592)
- METHYLENE-BIS-ORTHO-CHLOROANILINE  
 OCCUPATIONAL HAZARD (1543)



METHYLNITROSUREA  
   BRONCHIAL ADENOMA, ORGANOTROPISM,  
   MOUSE (1590)  
   NERVOUS SYSTEM TUMOR, RAT (1589)  
 MICROSOME  
   DRUG METABOLIZING ENZYMES, POLYCYCLIC  
   HYDROCARBONS, PHENOBARBITAL,  
   INDUCTION, REPRESSION, THEORETICAL  
   MODEL (1578)  
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   MAMMARY, VIRUS-LIKE PARTICLE, HUMAN  
   (1693)  
 MITOCHONDRIA  
   HEPATIC, X-RAY, THERAPY, RAT (2156)\*  
 MITOCHONDRIAL RNA  
   HELA CELLS (2183)\*  
 MITOSIS  
   CELL CYCLE, CARCINOGENESIS, REVIEW  
   (1514)  
   INHIBITION, KILHAM RAT VIRUS, RAT  
   EMBRYO CELL (1702)  
   RADIOAUTOGRAPHY, SOLID TUMORS (1972)  
 MIXED TUMOR  
   H102E, HAMSTER (2032)\*  
 MORTALITY  
   CANCER  
     ATOMIC BOMB SURVIVOR (1662)  
     NORTH AMERICA, WESTERN EUROPE  
     (1917)  
 MULTIPLE MYELOMA  
   LEUKEMIA, OCCUPATIONAL HAZARD,  
   INCIDENCE, FARMER, UNITED STATES  
   (1932)  
   PATTERNS, HUMAN (2198)\*  
 MURINE LYMPHOCYTES  
   BLASTOGENIC EFFECT, PHYTOHEMAGGLUTININ  
   MOUSE (2098)\*  
 MURINE TUMOR  
   CELLS, SYNTHESIS, L-ASPARAGINE (2047)\*  
 MUTAGEN  
   CHEMICAL, CHROMOSOME ABERRATION,  
   SPERMATOGONIA, MOUSE (1644)\*  
   DNA, SPECIFICITY (1634)\*  
 MUTAGENICITY  
   N-ALKYL-N'-NITRO-N-NITROSOGUANIDINES,  
   HIGHER PLANTS (1642)\*  
   10-DIMETHYL-1,2-BENZANTHRACENE,  
   BENZO(A)PYRENE, DNA LINKAGE (1572)  
   DIMETHYLNITROSAMINE, METABOLIC  
   PRODUCT, LIVER ENZYME, MOUSE (1584)  
   DRUG TESTING (1619)\*  
   4-NITROQUINOLINE-1-OXIDE,  
   BACTERIOPHAGE (1595)  
   PHENTHYL NITROGEN MUSTARD, ETHYLENE-  
   IMINOPYRIMIDINE, ASPERGILLUS NIDULAN  
     (1653)\*  
 MUTATION  
   IMMUNITY, NEOPLASM, CHEMOTHERAPY,  
   REVIEW (1522)\*  
   ROUS SARCOMA VIRUS, ADENOSINE  
   3',5'-MONOPHOSPHATE, TRANSFORMATION  
   CONTROL (1737)  
 MYCOTOXIN  
   ONCOGENESIS, BLOOD DISEASE (1539)  
 MYELOCYTES  
   CELL PROLIFERATION, HUMAN (1975)  
 MYELOID LEUKEMIA  
   CRISIS, HUMAN (2143)\*  
 MYELOMA  
   CELL  
     EGG SUBCLASS ASSEMBLY, MOUSE  
     (1806)  
     IGE, SYNTHESIS, SECRETION, HUMAN  
     (1809)  
     IGA, PROTEIN, STRUCTURAL CHARACTER-  
     ISTICS, MOUSE (1866)\*  
     IGA PRECIPITATION (2046)\*  
     POLYPEPTIDE CHAINS, DETECTION, HUMAN  
     (2090)\*  
   PROTEIN  
     IGG, ANTIBODY SPECIFICITY, HUMAN  
     (1838)  
     PHOSPHORYLCHOLINE, AFFINITY,  
     LABELING, MOUSE (1870)\*  
     ULTRASTRUCTURE, IRRADIATION, HUMAN  
     (2028)\*  
 MYELOPROLIFERATIVE DISORDER  
   HEMATOLOGY, SERUM LYSOZYME, B12,  
   BINDING CAPACITY (1966)  
 MYOBLASTOMA  
   ELECTRON MICROSCOPY (2010)  
   MULTILOCAL, FAMILIAL, HUMAN (2136)\*  
 MYOSARCOMA  
   HISTOLOGY, HUMAN (2092)\*  
 NASOPHARYNX  
   CANCER, CHROMOSOME, HUMAN (2021)  
   CARCINOMA, MORTALITY, TAIWAN (1927)  
 NEOPLASIA  
   EPIDEMIOLOGY, REVIEW (1530)\*  
 NEOPLASM  
   GALL BLADDER, INCIDENCE, IMMIGRANT  
   PATTERNS (1919)  
   HEMAPOIETIC CELLS, BONE MARROW,  
   INHIBITION, MOUSE (2077)\*  
   ISOENZYMES, HEMOBLASTOSIS, HUMAN  
   (2155)\*  
   LIVER, OPISTHORCHOSIS, INCIDENCE,  
   RUSSIA (1925)  
   LYMPHOCYTE, ACTIVITY, HUMAN (2126)\*  
   MAST CELLS, CAT (1992)

METASTASES, BONE, SCAN, HUMAN (2071)\*  
 MUTATION, IMMUNITY, CHEMOTHERAPY,  
 REVIEW (1522)\*  
 PRIMARY, CHROMOSOME, HAMSTER (1913)\*  
 SPONTANEOUS, MICE (2012)  
 NEOPLASTIC  
 HEMOBLASTOSIS, LACTATE DEHYDROGENASE,  
 HUMAN (2042)\*  
 NEPHROBLASTOMA  
 WILM'S TUMOR, RAT (2134)\*  
 NEPHROMA  
 CONGENITAL, RENAL STRUCTURE INDUCTION,  
 HUMAN (1885)  
 NERVOUS SYSTEM  
 CARCINOMA, INCIDENCE, SENEGAL (1945)\*  
 TUMOR  
 ETHYLNITROSOUREA, RAT (1588)  
 METHYLNITROSOUREA, RAT (1589)  
 NEURINOMA  
 ENZYMES, SERUM, DOPAMINE, MOUSE  
 (2095)\*  
 NEUROBLASTOMA  
 FAMILIAR OCCURRENCE, CASE REPORT  
 (1939)\*  
 GROWTH STIMULATION, DOPAMINE EFFECT  
 REVERSAL, IPRONIAZID, MOUSE (1631)\*  
 NEUROSARCOMA  
 INDUCTION, N-NITROSOBUTYLUREA,  
 HAMSTER (1649)\*  
 4-NITROQUINOLINE-1-OXIDE  
 CELL TRANSFORMATION, MAMMAL (1597)  
 DNA REPAIR SYNTHESIS REDUCTION,  
 XERODERMA PIGMENTOSUM (1596)  
 MUTAGENICITY, BACTERIOPHAGE (1595)  
 NITROSAMINE  
 DISTILLED SPIRITS, ESOPHAGEAL  
 CARCINOMA, EAST AFRICA (1583)  
 N-NITROSAMINE  
 PHOTOLYTIC DECOMPOSITION (1647)\*  
 NITROSO COMPOUNDS  
 FORMATION, NITRITE REACTION, CREATINE,  
 CREATININE (1544)  
 N-NITROSOBUTYLUREA  
 LEUKEMIA, BIOLOGICAL PROPERTIES, RAT  
 (1628)\*  
 NEUROSARCOMA INDUCTION, HAMSTER  
 (1649)\*  
 NITROSOGUANIDINE  
 SINGLE STRAND DNA BREAKS, HAEMOPHILUS  
 INFLUENZAE (1540)  
 NITROSOMETHYLUREA  
 LEUKEMOGENESIS, IMMUNODEPRESSION,  
 MOUSE (1610)\*  
 TRANSPLACENTAL BLASTOGENESIS, MOUSE  
 (1607)\*  
 NUCLEAR PROTEIN  
 SYNTHESIS, LIVER, BERYLLIUM, RAT  
 (1538)  
 NUCLEIC ACID  
 SMALL MOLECULES, INTERACTION,  
 CIRCULAR DICHROISM (1549)  
 SYNTHESIS  
 LIVER  
 AGING, CAFFEINE, RADIATION,  
 MOUSE (1639)\*  
 KIDNEY, DIMETHYLNITROSAMINE,  
 RAT (1587)  
 REVERSIBLE ALTERATION, THERMAL  
 BURN, HUMAN (1683)\*  
 NUCLEOPROTEIN  
 ONCOGENIC INFECTIOUS, STAGES OF  
 CANCERIZATION, UTERINE CERVIX, HUMAN  
 (1894)  
 NUCLEUS  
 ABERRATION, MALIGNANCY ASSOCIATED  
 CHANGES, CLASSIFICATION, HUMAN  
 (1891)  
 NUTRITION  
 DEFICIENCY, TUMORIGENESIS, REVIEW  
 (1502)  
 OCCUPATIONAL HAZARD  
 CUTTING OIL, HUMAN, REVIEW (1506)  
 LUNG CARCINOMA, RADON IRRADIATION  
 (1691)\*  
 METHYLENE-BIS-ORTHO-CHLOROANILINE  
 (1543)  
 OIL  
 CUTTING, OCCUPATIONAL HAZARD, HUMAN,  
 REVIEW (1506)  
 ONCOGENESIS  
 6-HYDROXYTESTOSTERONE,  
 DELTA 3,5-CHOLESTADIENE-7-ONE,  
 DELTA 4-CHOLESTENE-3,6-DIONE, MOUSE  
 (1545)  
 MYCOTOXIN, BLOOD DISEASE (1539)  
 ORAL CONTRACEPTIVE  
 BREAST TUMOR, INCIDENCE, UNITED STATES  
 (1922)  
 MAMMARY CANCER (1600)  
 OSTEOSARCOMA  
 IRRADIATION, HEREDITY, TRANSMISSION,  
 REVIEW (1518)\*  
 PHENOTYPES, TUMOR, SYNOVIAL SARCOMA  
 (1952)  
 OVARIAN  
 SARCOMA, HUMAN (2153)\*  
 TUMOR, ELECTROPHORESIS, PROTEINS,  
 HUMAN (2107)\*  
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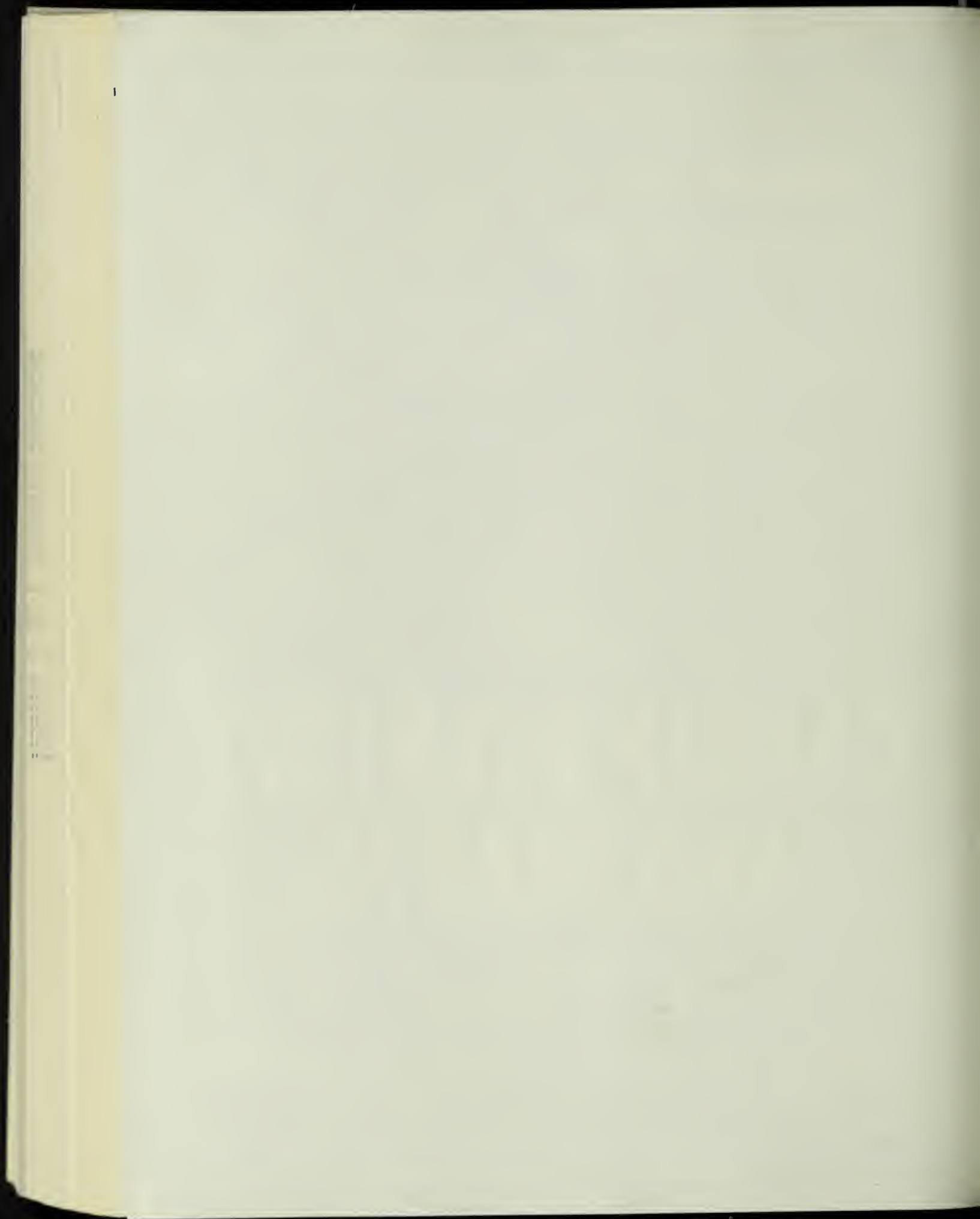
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# **CARCINOGENESIS ABSTRACTS**

**National Cancer Institute**

**U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • National Institutes of Health**





# CARCINOGENESIS ABSTRACTS

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## PREFACE

*Carcinogenesis Abstracts* is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred-fifty abstracts and three-hundred-fifty citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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## LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

## ABBREVIATIONS USED IN ABSTRACTS

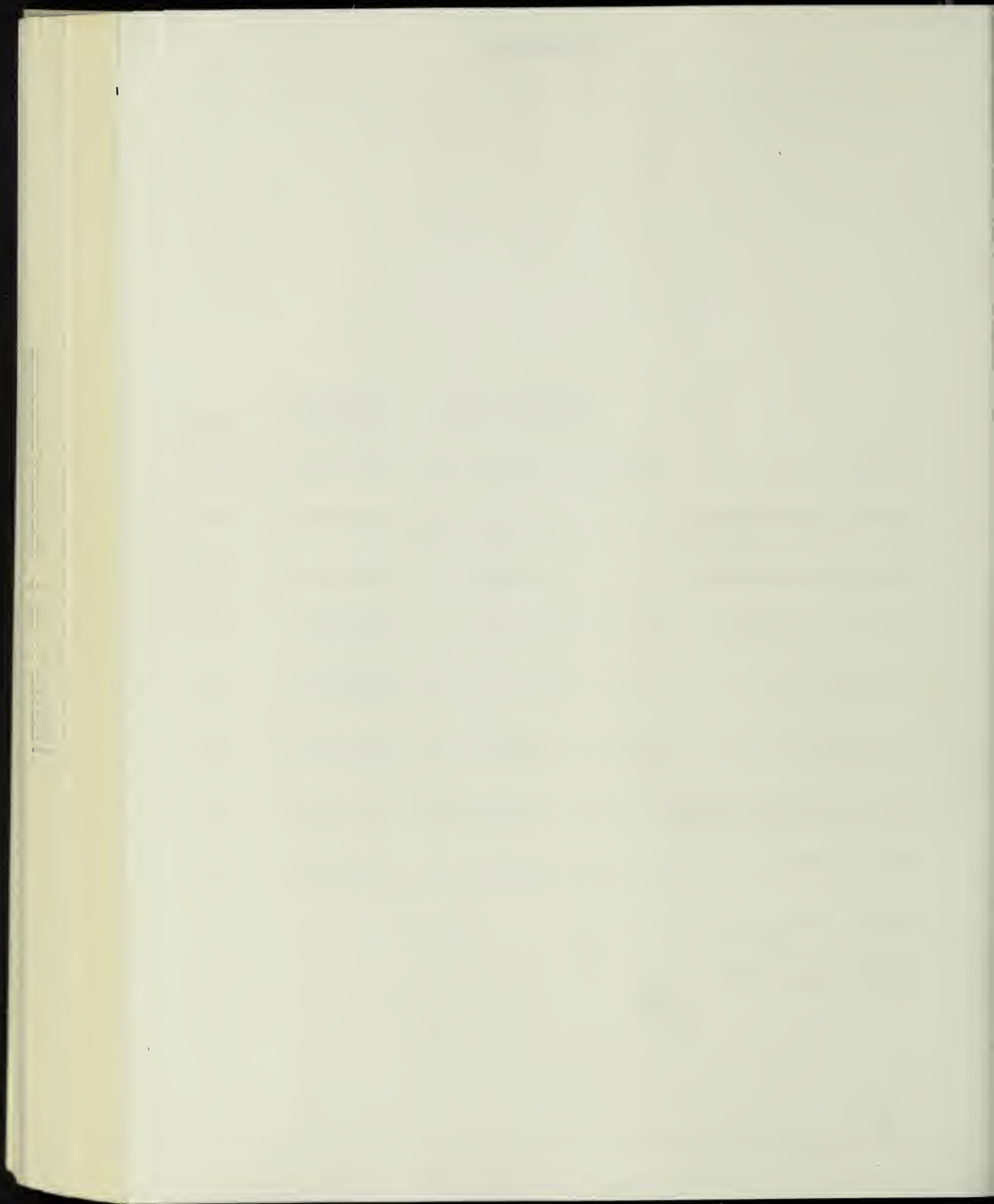
adrenocorticotrophic hormone	mg	milligram(s)
adenosine diphosphate	min	minute(s)
adenosine monophosphate	ml	milliliter(s)
adenosine triphosphate	mm	millimeter(s)
degrees centigrade	MTD	maximum tolerated dose
centimeter(s)	ng	nanogram ( $10^{-9}$ )
central nervous system	pg	picogram ( $10^{-12}$ )
counts per minute	p.o.	orally
deoxyribonucleic acid	ppm	parts per million
for example	r	Roentgen
gram(s)	RBC	red blood cells (erythrocytes), red blood count
microgram(s)	resp.	respectively
hour(s)	Rev.	review (only in citations)
intramuscular	RNA	ribonucleic acid
intraperitoneal	s.c.	subcutaneous
international unit(s)	sec	second(s)
intravenous	U	unit(s)
kilogram(s)	UV	ultraviolet
median lethal dose(s)	WBC	white blood cells (leukocytes), white blood count
meter(s)	wk	week
molar	wt	weight
milliequivalent(s)	yr	year(s)
millimolar		
micromolar		
milli-,microcurie(s)		





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2201 ADVANCES IN BIOCHEMISTRY OF ONCOGENIC RIBOVIRUSES. (Fr.) Larsen, C. J. (Res. Inst. Leukemia, Paris, France). *Pathol Biol* 19(9/10): 523-530, 1971.

The discovery of two polymerases within RNA viruses, one with marked specificity for RNA, the other for DNA, and of an intraviral endonuclease, is described. The specific polymerase for RNA was identified in almost all oncogenic RNA viruses and its presence is not related only to certain viral preparations but also extends to animal viruses and to viruses from the supernatant liquid of cell cultures. The enzyme isolated by treating the virus with a detergent (Triton X-100), has the same density as the nucleoside, indicating that it forms part of it. The protein nature of the enzyme was revealed when its activity was eliminated by proteolytic enzymes. The reaction of the DNA polymerase is very specific and requires the presence of 4-nucleoside triphosphates for best yield. Magnesium and manganese also potentiate the reaction up to 100-fold but not in two nononcogenic viruses (Visna and SV5 viruses) which possessed polymerase activity. The product synthesized *in vitro* is DNA. This was confirmed not only by its density but also by analysis and molecular hybridization. The polymerase specific for DNA was found in the Rous, Moloney, Rauscher and other viruses (it probably occurs in all systems) and can be detected *in vitro* by the addition of DNA of exogenous origin. The enzyme responds to a great variety of substrates; it is as yet unclear whether the enzyme consists of one or two proteins. The newly-discovered endonuclease was discovered when DNA from the phase T was incubated with Rous virus preparations. The resulting decomposition of the material was due to an endonuclease since no acid-soluble product was formed. These findings would seem to support Temin's provirus theory which postulates that viral RNA is transformed into one or several molecules of DNA. This DNA is then integrated into the cell genes during cell division, which ensures survival of virus information even if this information is not expressed. Following the discovery of DNA polymerase activity in leucocytes of leukemic individuals it was thought that this could serve as a diagnostic biochemical test and as a therapeutic criterion. Lately, however, the discovery of these enzymes has also been reported in *in vitro* cultures from healthy individuals. (42 references.)

2202 IMMUNOLOGIC ALTERATIONS IN CHRONIC MALIGNANT LYMPHADENOPATHIES. (Sp.) Bachmann, J. E. (Nat'l. Med. Acad., Buenos Aires, Argentina), Sen, M. Braun and L. C. G. de Conesa. *Medicina (Buenos Aires)* 31(1):56-70, 1971.

Immunologic phenomena occurring in patients with chronic malignant lymphadenopathy are reviewed. Immunologic alterations are divided into three groups: thymus-independent, immediate type hypersensitivity, occurring in patients with myeloma; thymus-dependent, hypersensitivity of the delayed type, occurring in patients with Hodgkin's disease; and alterations of the combined type occurring in

patients with chronic lymphoid leukemia. Qualitative and quantitative dysimmunoglobulinemia, alterations in the response to phytohemagglutinin, alterations in the response to heterogenetic antigens, alterations of delayed type hypersensitivity, and alterations of immediate and delayed type hypersensitivity against homologous antigens, circulating, and cellular antibodies are discussed. Clinical, *in vivo* and *in vitro* data available in the world literature are used to illustrate the discussion. (176 references)

2203 RADIATION AND LEUKEMIA MORTALITY: PROOF OR SPOOF. (E.) Barber, D. E. (Sch. Public Hlth., U. Minnesota, Minneapolis). *Minn Med* 55(3): 215-219, 1972.

The relationship between radiation exposure and leukemia incidence is discussed. Specific site surveys in Oregon, Washington and Minnesota are compared to the nationwide leukemia mortality rates. Findings indicate that national dose rates from fallout were high in the years 1958-59 and 1962-63. However, expected increased mortality rates 5-10 yr later were not reflected in actual fact. Figures presented show a leveling off and decrease of leukemia mortality from 1955 to 1963 in all age groups except for those over 75 years. With the exception of short-term fluctuations in specific areas where nuclear generators are in operation, it is proposed that the downward trends in leukemia mortality are indicative of an inverse relationship between exposure and leukemia. (14 references)

2204 IMMUNOLOGIC FEATURES OF MALIGNANT TUMORS. (Ger.) Scheurlen, P. G. (Saar U., Homburg, Germany). *Med Welt* 22(33-34):1257-1261, 1971.

Clinical and experimental evidence is reviewed regarding characteristics of cancer cells against which the organism mobilizes specific immunologic defense reactions and the result of inhibition of immunologic defense. Malignant tumors in which specific immunoreactions were detected include the Burkitt lymphoma, the chorion epithelioma, the malignant melanoma, the neuroblastoma, the osteosarcoma, other sarcomas, intestinal adenocancers and primary liver cell cancer. Over the past 15 years much information on antigenic properties of tumors was derived from animal experiments involving isologous animals in which specific tumor antigens were detected. Experiments disclosed that the growth of tumors was modified by a change in immunologic defense; that a critical tumor cell mass existed; that the animals reacted to tumor antigens, mostly by cellular immunoreaction, and that an enhancement of resistance by antibodies was possible. An experimental tumor, no matter how induced, evoked an immunologic reaction which was directed specifically against the tumor cells when transplanted on an isologous animal, thus proving that tumor cells possess specific antigens. Immunologic defense can be enhanced by treating animals before transplantation with killed tumor cells, i.e., by immunization. A critical tumor cell mass exists against which im-

munologic defense is still effective. Immunologic reactions against tumor cells have also been detected *in vitro*. Experiments involving the incorporation of  $^{14}\text{C}$ -thymidine in PHA-stimulated lymphocytes in healthy subjects, in patients with stomach cancer and with lymphogranulomatosis, and in other experiments confirmed the existence of a relationship between tumor growth and inhibition of the immunologic system. This was also confirmed on laboratory animals by immunosuppression (by thymectomy, irradiation, steroids, etc.). Tumors also have an immunosuppressive effect of their own. It is still unresolved whether cytostatic treatment of autoimmune diseases with azathioprin enhances the formation of autochthonous tumors, but there is some statistical evidence to that effect gathered in experiments on kidney transplant patients. All attempts to check the growth of malignant tumors by intensified immunoreaction brought little success and then only in individual cases. (No references)

- 2205 THE H POLYMERASE: A FURTHER STEP TOWARDS THE VIRAL ORIGIN OF HUMAN LEUKEMIA. (Fr.)  
Driessens, J. (Cancer Research Inst. Lille, France).  
*Lille Med* 16(6):788-791, 1971.

Polymerase H (H=hybrid), an enzyme polymerizing DNA subunits under RNA influence, was found to be active in the biochemical evolutionary cycle of RNA viruses. The fundamental assumption of molecular biology which calls for a strictly irreversible DNA-RNA cycle in all cells is thus contradicted. The biochemical evolutionary cycle is thought to proceed from intracellular penetration of the virus to intracellular viral RNA, to polymerase H, to viral RNA plus complementary DNA, to messenger RNA, to ribosomes, to viral proteins, and to virions. In this interpretation of the cycle, polymerase H is indispensable. The unfolding of the first virus replication stage is not blocked by the classical inhibitors of protein synthesis which would prevent polymerase H synthesis if it was formed by the virus since it is already in existence before the blockage in the cell or in the infecting virus. Cellular transformation by the RNA virus is the consequence of the inclusion of a DNA fraction into the cellular genome which is not directly viral but complementary to viral RNA. The practical implications of the above are that if human leukemia is of viral origin then it is probably caused by an RNA virus, as in animal leukemia, and if this is so then the viral cycle requires the presence of polymerase H for its completion. If polymerase H is then present, it is proof of the presence of the causative virus. (No references)

- 2206 VIRAL AETIOPATHOGENESIS OF TUMORS. (E.)  
Klein, E. (Karolinska Inst., Stockholm, Sweden). *Boll Inst Sieroteropico Milanese* 50(3): 140-151, 1971.

With the development of histocompatible antigens has

come a better understanding of oncogenic processes and a continuing search for the oncogenic agents in tumors of unknown etiology. Experimental systems have allowed wider exploration into the area of preventive techniques through vaccination against oncogenic processes. Consideration of the incidence of common antigens in tumor groups has been regarded as indicative of viral etiology. Continued efforts in regard to the viral etiology of tumor groups are being exerted to distinguish between passenger viruses and oncogenic agents. Extensive studies using Burkitt lymphoma (BL) cells have led to clarification of the relationships between Epstein Barr Virus and the membrane antigens. Studies on the nature of the membrane antigen, particularly the specification by viral or cellular genome, are being carried out. Distinction between the real or spurious negative results in serological anti-EB reactivity in a portion of the human population are being determined. The role of test artifacts is under scrutiny. Serological patterns which may be disease-related are currently being correlated to prognosis. Geographic distribution of diseases with a ubiquitous virus and the relationship to transmission co-factors is presented. Preliminary evidence indicates the possible existence of closely related but biologically different viruses, with differences in oncogenic power and target tissue preference. Methodologic difficulties currently prevent full assessment of cell-mediated immunity, as seen in the BL studies. Presently feasible methods allowing quantitative assessment of cell bound immunity and the synergistic or antagonistic action of humoral antibodies have yet to be developed for practical application. (109 references)

- 2207 CHEMICAL CARCINOGENS. (E.) Searle, C. E.  
(U. Birmingham, Med. Sch., England). *Chem Industr* 5(3):111-116, 1972.

The range of known chemical carcinogens has grown enormously since initial experiments have shown that polycyclic aromatic hydrocarbons are carcinogens. Increased knowledge of both natural and synthetic carcinogenic agents raises the real possibility that cancer can be prevented. Agents such as viruses, UV, X-ray,  $\gamma$ -irradiation, and numerous environmental conditions are not only recognized as causal factors of this disease, but are the focus of exhaustive research. Unfortunately, the recognition of causal factors has not always resulted in practical measures to remove the carcinogenic hazards, especially within the field of chemistry. Collaborative investigations have pinpointed numerous compounds such as aromatic amines, nitro compounds, azo dyes and alkylating agents which are hazardous to investigators. Moreover, regulations have been established to prevent the introduction and use of harmful materials by persons involved in industrial or technological activities. The need for continued monitoring of actual and potential carcinogenic hazards is detailed, in light of relevance to current activities in the field of chemistry. (23 references)



2208 IMMUNOSUPPRESSION, INTEFERON, AND VIRAL INFECTIONS. (E.) Glasgow, L. A. (U. Utah Coll. Med., Salt Lake City). *Fed Proc* 30(6):1846-1851, 1971.

A review of the work involving the influence of immunosuppressive agents on the production or release of interferon is given. The capacity of the living animal to respond to a variety of inducing agents with the production of interferon is extremely resistant to suppression. The effect of immunosuppressive agents that are cytolytic for the lymphoid cell population, such as x-irradiation, immunosuppressive drugs and antilymphocyte sera, is dependent upon the nature of the interferon-inducing agent. It was concluded that lymphocytes (at least cells of lymphoid origin) were involved in the interferon response to the myxoviruses and possibly Tilorone, but did not appear to be important factors in the majority of viral infections. (38 references)

2209 CANCER IN FIVE CONTINENTS. (E.) Doll, R. (Radcliffe Infirmary, Oxford, England). *Proc Roy Soc Med* 65(1):49-55, 1972.

Current epidemiologic studies leading to quantitative correlation between cancer and the prevalence of a suspected agent are reported. Data sources such as clinical and pathological series are used to demonstrate the existence of differences in the geographic distribution of cancer. The publication of mortality rate data and cancer registration information provides a high degree of precision in reporting worldwide incidence of cancer. Limitations in data analysis are presumed to be caused by the inaccuracy of some of the figures submitted by medical services and the lack of histologic verification and of differentiation of tissues. Data point to the frequent occurrence of five types of cancer: 1) esophageal; 2) gastric; 3) colonic; 4) bronchial; and, 5) breast. Reference is made to the interplay between genes and the environment and the contribution that these factors make to the incidence of occurrence of specific types of tumors within selected populations. (26 references)

2210 LOW DOSE RADIATION CANCERS IN MAN. (E.) Stewart, A. (Dept. Soc. Med., U. Oxford, England). *Advances Cancer Res* 14:359-390, 1971.

This study deals with the possibility of confirming or refuting theories based on the assumption that in some circumstances a diagnostic X-ray can be the sole initiator of a malignant disease. The ongoing nature of the Oxford Study on obstetric radiography provides data on collecting and processing techniques which recognize the hazards involved in the use of X-rays during pregnancy. Information gathered allows the conversion of a dose-response curve based on numbers of films into one based on estimated fetal doses. An analysis of cohort risk indicates a trend toward

safer obstetrical X-ray examination. Cancer-latent period is discussed in light of the age of onset of neoplasms in juveniles and classification by cell type and X-ray experiences. The tissue-destructive effect of radiation exposure is considered to be highly variable; some individuals die from the septic complications of acute exposure while others remain in perfect health until they develop leukemia, as typified by survivors of atomic bomb explosions. The recognition of pneumonic complications of childhood infections during the two years preceding onset of leukemia establishes a relationship between infections and leukemia. Data, clearly indicate that in the case of radiation, a threshold situation exists in relation to the whole-body exposure. Sooner or later the rising dose demands the production of new cells to replace those destroyed by radiation. At this point, mutant stem cells are given the chance to infiltrate bone marrow and other myelocyte source areas. (52 references)

2211 MORPHOLOGICAL EVIDENCE FOR IMMUNE RESPONSE TO BREAST CANCER: AN HISTORICAL REVIEW. Berg, J. W. (Natl. Cancer Inst., Bethesda, Md.). *Cancer* 28(6):1453-1456, 1971.

This report reviews the current activities and status of the morphologic evidence for an immune response in patients with breast cancer. Techniques for recognizing immunity were either lacking or primitive during the late 1950's and 1960's. Patients in whom "spontaneous" regression of melanomas, both primary and metastatic, had occurred showed no prominent round cell reaction. The tumor cells seemed to fade away and if such disappearance is due to immunity, it is one without morphologic traces. Similar problems existing in regard to lymph node reactions are discussed. Conditions that are a sign of resistance in one situation are a sign of immunity failure in another; thus, no morphological reactions can presently be considered universal markers of immune response. At the present time it is thought that the closest morphologists may come to seeing immunity is to see hyperplasia of some elements of the immune system. Round cells in tumors can be thought of in this way, as can certain lymph node changes such as lymphoid infiltration of breast cancer as a sign of host rejection of the cancer. Behavioral changes of the cancer that might be produced by host immunity are listed as: 1) Retarded growth of metastases; 2) Decreased number of successful metastases; 3) Retarded growth of primary invasive tumor; 4) Reduced invasiveness; and, 5) Suppression of dysplastic clones. Although reference to plasma cell aggregation at the tumor margin as a sign of host resistance is made, it is noted that large cancers in this condition have failed to kill. Arguments against certain morphologic patterns being a signal of resistance in the host are presented. Recent work with skin window tests to measure a patient's hypersensitivity to cancer is discussed, in addition to histiocytosis as it is related to cell-mediated immunity. (35 references)

- 2212 IMMUNITY TO MALIGNANT DISEASE IN MAN.  
(E.) Fairley, G. H. (St. Bartholomew's  
Hosp., London). *Brit J Hosp Med* 6(5):633-634,  
636,641-644, 1971.

This report reviews the current status of research into tumor-associated antigens in man. Both direct and indirect evidence for the existence of these antigens is presented. Numerous reports establish the fact that in patients with immune-deficiency diseases (hypogammaglobulinemia, Wiskott-Aldrich and Chediak-Steinbrinck-Higashi syndromes, etc) there is an increased incidence of malignant disease. Further evidence for an accelerated rate of malignancy in patients with impaired immunity comes from graft experiments in man. The subcutaneous transplantation of human cells into healthy persons invariably results in transient growth followed by complete regression. Changes observed in lymphoid cell population in the peripheral blood of patients with Hodgkin's disease were identical with those found under conditions of known antigenic stimulation. This is taken to represent an immunologic reaction by the patient against his own disease. Evidence is accumulating which points to a host reaction existing in malignant melanoma; indications suggest this reaction could well be immunologic. Investigations seeking to establish the presence of these antibodies are in progress. Possible methods of influencing tumors by immunologic means through stimulation of the reticuloendothelial system, utilization of non-specific lymphoid cells, immunization with tumor-associated antigens and use of specifically stimulated lymphoid cells are discussed. At the present time, immunotherapy in no way replaces standard methods of treatment, and it is suggested that it be used only as an adjuvant for the removal of residual malignant cells after other forms of treatment have been used. (103 references)

- 2213 BCG IN CANCER AND LEUKEMIA. (E.) Rosenthal,  
S. R. (U. Illinois, Inst. Tuber. Res.,  
Chicago). *Bull de L'Institut Pasteur* 70(1):29-50,  
1972.

This report reviews the role of Bacillus of Calmette and Guérin (BCG) as an antigen. In recent studies discussed here, the immunologic mechanisms active against neoplasm, and the stimulator function of BCG are considered in specific and nonspecific context. The advantage in using BCG over other reticuloendothelial system stimulating agents is that it has been used in over a half billion human subjects with safety. Additionally, being an attenuated organism, it multiplies in the human host and is effective for long periods of time. Recommendation for broader use of BCG vaccination is made, especially in the course of a remission in acute leukemia or Hodgkin's disease, and following surgical removal of tumors. (56 references)

- 2214 THE CHANGING PATTERN OF RETINOBLASTOMA.  
(E.) Anonymous. *Lancet* (7732):1016-1017,  
1971.

Retinoblastoma is reported to be responsible for approximately 1% of all deaths from cancer in early childhood and for about 5% of blindness in children. The survival of bilaterally-affected individuals has contributed to recent verification of familial frequency. Indications point to an autosomal dominant gene as a causal factor, with the occurrence of a fresh mutation possible in some instances. Aberrations at certain loci in the D chromosome are discussed. Rapid advances in early diagnosis and effective treatment of patients with retinoblastoma are responsible for the longer survival rates occurring in this group. The effect of longer survival is discussed in light of mutant gene transmission to offspring. The susceptibility of patients with retinoblastoma to carcinogenic agents, particularly radiation, is pointed out. The importance of genetic counselling for this condition is stressed. (14 references)

- 2215 INDUCTION OF MALIGNANT LYMPHOMAS BY N,N'-  
DIMETHYLNITROSOUREA IN ADULT MICE. (E.)  
Hiraki, S. (Okayama U. Med. Sch., Japan). *Gann* 62  
(2):135-137, 1971.

Studies on the carcinogenicity of N,N'-dimethylnitrosourea (DMNU) in adult male and female 8-10-wk-old C3Hf/Bi mice, and the possibility of producing nervous system tumors, are reported. The mice were injected s.c. weekly with 80 mg/kg body wt of DMNU; control mice received 0.2 ml of only 0.9% saline s.c. All 30 treated mice developed malignant lymphomas between 64 and 126 experimental days (average 89 days); no pathologic changes were seen in the ten control mice. All malignant lymphomas were lymphocytic or lymphoblastic with many starry-sky cells. White blood cells were found to decrease after DMNU treatment; these increased to subnormal level at a later period in the lifespan of the treated mice. Using electron microscopy the malignant lymphomas were found to consist of almost uniform lymphoblastic cells with scanty fibrous stroma; at the time of this report no virus particles have been found in the tumor cells. It is noted that DMNU induced malignant thymic lymphomas in 100% of the treated mice but did not induce any tumors of the nervous system.

- 2216 THE CELL CYCLE IN TUMOURS: AN EXAMINATION  
OF DATA GAINED BY THE TECHNIQUE OF LABELLED  
MITOSES. (E.) Steel, G. G. (Inst. Cancer Res.,  
Sutton, Surrey, England). *Cell Tissue Kinet* 5:87-100,  
1972.

Data obtained from a large number of investigations using the technique of labelled mitoses for tumor studies were analyzed by a process of computer simulations, the results of which are presented. The following topics are discussed in terms of both the present study and the extent of related knowledge about the intermitotic time of tumor cells: (1) analysis of labelled mitoses curves; (2) discrepancies found between theoretical and experimental labelled mitoses curves; (3) summary of results obtained on tumors in experimental animals; (4) labelled mitoses curves for human tumors; and (5) implications of a broad spread of intermitotic time. (44 references)



- 2217 OCCURRENCE OF TUMORS IN DOMESTIC ANIMALS: DATA FROM 12 UNITED STATES AND CANADIAN COLLEGES OF VETERINARY MEDICINE. (E.) Priester, W. A. (Nat'l. Cancer Inst., Bethesda, Md.) and N. Mantel. *J Nat Cancer Inst* 47(6):1333-1344, 1971.

Data on 8,634 tumors from 202,277 animals in 12 veterinary college-clinic hospitals in the United States and Canada are presented. Microscopic examination provided confirmation of tumors, with radiologic diagnosis being accepted for confirmation of primary bone tumors. Tumors were classified as benign, malignant, or malignancy not determined (MND). The most frequent tumor site for cattle was the eye; for dogs and horses, the skin, and for cats, the hemic and lymphatic systems. Tumors in cattle were found to have the most narrow spectrum of distribution by cell type, with the widest distribution being found in dogs. Only dogs and cattle showed any significant sex differential in tumors found. All four species showed an increasing risk with age for all tumors, as well as for malignant tumors alone. These data are quite consistent with what is generally known about tumors, and agree quite well with data already published concerning spontaneous tumors in domestic animals. (26 references)

- 2218 A STUDY OF CARCINOMA OF UTERINE CERVIX WITH SPECIAL REFERENCE TO ITS CAUSATION AND PREVENTION. (E.) Malhotra, S. L. (Med. Dept., South Eastern Railway, Calcutta, India). *Obstet Gynec Survey* 27(2):116-117, 1972.

The histories of 50 31- to 50-yr-old females with histologically proven carcinoma of the cervix (one adenocarcinoma, 48 squamous cell and one undifferentiated) seen in Calcutta hospitals were compared with histories of sociologically matched, normal, healthy women. There was no apparent correlation between carcinoma of the cervix and frequency of childbearing, circumcision of the husband, history of syphilis, socioeconomic status, or penile hygiene. The relatively earlier age of marriage of carcinoma patients (16.2 compared to 19.4 yr for controls) and the higher frequency of sexual intercourse (12.43 compared to 3.92 per month for controls) indicated a possible etiological role for these two factors. Since a higher pH was measured in seminal fluid from husbands who had frequent intercourse compared with a less alkaline pH of fluid from husbands who had infrequent intercourse, it was hypothesized that seminal fluid pH may be related to the etiology of cervical carcinoma. Decreased incidence of carcinoma of the cervix in women who employed barrier contraceptive devices and increased incidence in women using oral steroids were consistent with this latter hypothesis. (No references)

- 2219 RADIATION AND LUNG CANCER. (E.) Cihak, R. W. (Bur. Radio. Hlth., Atomic Bomb Casualty Commission, Hiroshima, Japan). *Human Path* 2(4):525-530, 1971.

The relationship between primary lung carcinoma and

radiation has long been studied. It was discovered initially when pitchblende and uranium miners and poison gas factory workers were found to have a high incidence of pulmonary neoplastic lesions due to inhalation of radioactive particles. External x-irradiation, however, does not have the same effect in all cases. Children exposed to large doses of x-rays and South Pacific adult humans accidentally exposed to atomic fallout did not show increased prevalence of pulmonary tumors. It was found that tumor incidence was actually decreased in the x-rayed animals when animals were exposed to high radiation doses. A study of atomic blast survivors from Hiroshima and Nagasaki, Japan, indicated that persons become susceptible to oncogenic effects when exposed to doses in excess of 128 rads. Current studies are being carried out to determine the effect of synergistic factors which may influence the interpretation of the Japanese data. (27 references.)

- 2220 CARCINO-EMBRYONAL ANTIGENS. (Dut.) Peeters, T. (Clin. Int. Dis., U. Leuven, Netherland) and G. Vantrappen. *Geneesk* 28(4):338-340, 1972. (13 references)

- 2221 FACTORS INVOLVED IN CARCINOGENESIS. (Fr.) Hoeffel, F. (No affiliation). *Gaz Med* 78(35):6295-6308, 1971. (No references)

- 2222 THE IMPORTANCE OF NITROSAMINES AS ENVIRONMENTAL CARCINOGENS. (Ger.) Stavrou, D. (Dept. Vet. Med., U. München, Germany). *Fortschr Med* 90(7):249-252, 1972. (24 references)

- 2223 REGIONAL VARIATIONS IN PRIMARY LIVER CANCER ON THE MARFIM COAST. (Por.) Anonymous. *Bol Inst Port Oncol* 38(9):1-3, 1971. (No references)

- 2224 BONE MARROW AND PERIPHERAL BLOOD CELL PROLIFERATION UNDER NORMAL AND LEUKEMIC CONDITIONS. (Rus.) Kozinets, G. I. (Ctr. Inst. Hemat. Blood Transf. Moscow, USSR) and G. L. Rapoport. *Probl Gemat* 17(2):55-62, 1972. (129 references)

- 2225 NEOPLASTIC AND PARANEOPLASTIC PERIPHERAL NERVE DISEASES. (Fr.) Garde, A. (No affiliation), J.-F. Savet and P. Trouillas. *Rev Prat* 21(31):4711-4720, 1971. (5 references)

- 2226 NEWS IN THE FIELD OF DERMATOLOGICAL ONCOLOGY. (Ger.) Nödl, F. (Skin Dis. Clin. U. Saar, Homburg, Germany). *Dtsch Med J* 23(2):139-141, 1972. (30 references)

- 2227 INDUCED CELLULAR CHANGES AND ONCOGENESIS. (Sp.) Marsili-Feliciangeli, F. (It. Hosp. Asmara, Etiopia). *Folia Clin Int (BARC)* 21(12):725-732, 1971. (No references)

- 2228 INTRACELLULAR DNA REPAIR - A NEW ASPECT OF CANCER RESEARCH. (Ger.) Magdon, E. (Inst. Cancer Res., Cer. Acad. Sci., Berlin) and H. Gummel. *Deutsch Gesundh* 27(9):385-397, 1972. (107 references)
- 2229 CANCER OF THE RECTUM. (Fr.) Girard, M. (No affiliation). *J Med Lyon* (1222):185-188,191, 1972. (No references)
- 2230 N-NITROSAMINES: FACTS AND FICTION. (Dut.) Schuller, P. L. (Lab. Chem. Food Res., Natl. Inst. Pub. Hlth., Bilthoven, Netherlands). *Voeding* 33(2):76-92, 1972. (159 references)
- 2231 CARCINOGENESIS, CANCER GROWTH, METASTASIS: VEGETATIVE FUNCTIONS OF AN UNDIVIDED ORGANISM. (Ger.) Schlitter, H. E. (Humboldt City Hosp., Berlin, Germany). *Ther Gegenw* 111(3):345-366, 1972. (36 references)
- 2232 INFECTIOUS MONONUCLEOSIS AND MALIGNANT LYMPHOPROLIFERATIVE DISEASES. (E.) Stevens, D. A. (Stanford U. Sch. Med., Calif.). *J Amer Med Assoc* 14(7):897-898, 1972. (14 references)
- 2233 MYELOMA: GENERAL FEATURES OF IMMUNOGLOBULINS IN KAHLER'S DISEASE. (Fr.) Suau, E. (No affiliation) and B. Mazieres. *Rev Med Toulouse* 8:53, 1972. (No references)
- 2234 EXPERIMENTAL CARCINOGENESIS DURING FETAL DEVELOPMENT. (Sp.) Ivankovich, S. (Ger. Cancer Res. Ctr., Heidelberg). *Folia Clin Int (BARC)* 21(12):711-716, 1971. (No references)
- 2235 CONSIDERATIONS ON THE PRESENCE OF A SPECIFIC VIRAL DNA REPLICATION REPRESSOR IN PAPOVA VIRUS-TRANSFORMED CELLS. (It.) Barbanti-Brodano, G. (Inst. Microbiol., U. Bologna, Italy) and M. La Placa. *G Mal Infett* 23(9):860-863, 1971. (30 references)
- 2236 AVIAN MYELOBLASTOSIS VIRUS: A MODEL FOR THE STUDY OF VIRAL LEUKEMIAS. (It.) Zanetti, M. (Inst. Microbiol., U. Bologna, Italy), M. Portolani, L. Foa and M. La Placa. *G Mal Infett* 23(9):865-873, 1971. (62 references)
- 2237 B-TYPE PARTICLE-INDUCED TUMORIGENESIS IN MICE AND HUMAN PATHOLOGY IMPLICATIONS. (It.) Squartini, F. (Inst. Path. Anat. Hist. U. Pisa, Italy). *G Mal Infett* 23(9):875-881, 1971. (87 references)
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- 2239 SOME ASPECTS OF RNA VIRUS-INDUCED ONCOGENESIS WITH SPECIAL REFERENCE TO CORRELATIONS AND RESULTS OBTAINED IN HUMAN PATHOLOGY RESEARCH: FUTURE PROSPECTIVES. (It.) Magrassi, F. (Med. Clin. Inst. U. Napoli, Italy), F. Coraggio, V. Coto, J. Georgiades, G. Galeota, A. D'Acunto, L. Cuccurullo, J. Nasti, A. Violante, P. Trovalusci Crateri and G. Catalano. *G Mal Infett* 23(9):899-922, 1971. (50 references)
- 2240 THE BIOCHEMISTRY OF NORMAL ACTIVATED CELL ENZYMES AND LEUKEMIC LEUKOCYTES: PART VIII. BIOCHEMICAL ALTERATIONS OCCURRING IN LYMPHOCYTES UNDER ACTIVATION CONDITIONS. (Pol.) Sznajd, J. (Inst. Clin. Chem., Krakow, Poland), B. Malkiewicz, J. Nas-kalski and J. Lisiewicz. *Przegl Lek* III 28(9):597-601, 1971. (85 references)
- 2241 RECENT EXPERIMENTAL DATA ON VIRAL CARCINOGENESIS IN RODENTS: EXPERIMENTAL INDICATIONS WHICH COULD BE REVEALING FOR THE PRESENCE OF VIRUS IN HUMAN TUMORS. (It.) Negroni, G. (Imp. Cancer Res. Fund, Mill Hill Lab., London, England). *G Mal Infett* 23(9):823-833, 1971. (74 references)
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- 2299 CHANGES IN THE ACTIVITIES OF GLUCOSE-6-PHOSPHATASE, ALDOLASE, AND ALKALINE PHOSPHATASE DURING AZO-DYE CARCINOGENESIS. (E.) Kaneko, A. (Sapporo Med. Coll., Japan), K. Dempo, T. Iwasaki and T. Onoe. *Gann* 63(1):31-39, 1972.

Male Wistar rats were put on a regimen of dietary 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB), as follows: 15 rats were fed carcinogen-free diet (controls); 145 rats in three groups were fed a diet containing 0.06% 3'-Me-DAB for eight or 12 wk, followed by basal diet for three days or one, two, four or eight wk. Rats were killed and liver fragments were prepared for assay of glucose-6-phosphatase (G-6-Pase), alkaline phosphatase, and aldolase activities in liver cells regenerating after 3'-Me-DAB feeding. After 3'-Me-DAB feeding many liver cells degenerated markedly and some disappeared. Subsequently, proliferated cholangiolar cells replaced degenerated liver cells. G-P-Pase activity in livers of 3'-Me-DAB-fed rats decreased rapidly after carcinogen feeding; by the third wk, G-6-Pase activity was 25% of controls. By the sixth wk, it increased to 40% of controls and thereafter it showed small fluctuation. After cessation of 3'-Me-DAB feeding at eight wk, G-6-Pase increased, but it never attained control values. Aldolase activity was measured using both fructose diphosphate (FDP) and fructose monophosphate (FMP) as substrates. The pattern of aldolase activity with FMP resembled that of G-P-Pase activity. The degree of inhibition by 3'-Me-DAB of aldolase activity with FDP was less than that of aldolase with FMP. Muscle-type aldolase increased 4-8 wk after 3'-Me-DAB feeding. Alkaline phosphatase activity was measured with and without the addition of  $MgCl_2$  in the medium. Alkaline phosphatase activity with  $MgCl_2$  fluctuated in the same pattern as that of FDP activity of aldolase, while activity without  $MgCl_2$  increased and maintained a higher level than control between 4-8 wk after 3'-Me-DAB feeding. Like G-6-Pase and aldolase with FMP, alkaline phosphatase recovered after eight wk in 3'-Me-DAB fed animals but did not recover in the control group.

- 2300 FLUCTUATION OF VARIOUS CELL POPULATIONS AND THEIR CHARACTERISTICS DURING AZO-DYE CARCINOGENESIS. (E.) Iwasaki, T. (Sapporo Med. Coll., Hokkaido, Japan), K. Dempo, A. Kaneko and T. Onoe. *Gann* 63(1):21-30, 1972.

Two hundred male Wistar rats were fed on a diet containing 0.06% 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB); changes in various liver cell populations were observed by light and electron microscopy up to 33 wk after initiation of 3'-Me-DAB feeding. Hydropic degeneration of hepatocytes appeared in the first wk; some degenerative hepatocytes were markedly hypertrophied. Degenerative cell proliferation peaked in the fourth wk. After two wk of 3'-Me-DAB, oval cells began to proliferate around the portal area of the liver. Proliferation of oval cells reached a maximum in the fourth wk, when oval cells occupied about half of liver lobules. Small basophilic cells began to appear in livers in the fourth wk among proliferating oval cells at the periportal areas of liver lobules; the increase of

basophilic cells was followed by decreases in oval cells and in degenerative original hepatocytes. Basophilic cells (renewed hepatocytes) came increasingly to resemble normal hepatocytes. By nine to 11 wk, hepatic lobules were almost completely occupied by renewed hepatocytes. Glucose-6-phosphatase (G-6-Pase) activity decreased rapidly after 3'-Me-DAB ingestion (25% of normal after three wk). By six wk, G-6-Pase activity increased to 40% of normal, and showed only slight fluctuation thereafter. Protein-bound dye content decreased during the first five wk of 3'-Me-DAB feeding. The content began to increase again by the eighth or ninth wk, and thereafter decreased again. Liver weight decreased in the fourth wk when degeneration of original hepatocytes was marked. After that, liver weight recovered gradually, following the growth of renewed hepatocytes. By 14 wk, liver weight showed a slight decrease again.  $\alpha$ -Fetoprotein began to appear after four wk of 3'-Me-DAB, and increased to the seventh wk, after eight wk,  $\alpha$ -fetoprotein disappeared.

- 2301 THE EFFECT OF THE INGESTION OF p-DIMETHYLAMINOAZOBENZENE (DAB) AND OF 3'-METHYL-DAB ON THE ACTIVATION POWER OF DAB AND ON THE AZOREDUCTION OF RAT LIVER MICROSOMES. (Fr.) Decloitre F. (Inst. Cancer Research, Villejuif, France), M. Meunier and M. Auffret. *C R Acad Sci [D](Paris)* 274(5):776-779, 1972.

Two aspects of the metabolism of azocarcinogens, their activation power, and their effect on azoreductase activity, were studied by feeding three groups of four to five wk-old Sprague-Dawley male rats with a base ration, a base ration plus 0.06% DAB, and a base ration plus 0.06% 3'-methyl-DAB. The fixation of  $^{14}C$  DAB-metabolites to DNA in the presence of microsomal fraction was subsequently determined by the Meunier and Chauveau method, and azoreductase activity was determined as a function of feeding time. In the control group of rats  $^{14}C$  DAB fixation to DNA decreased rapidly in the first few weeks. Animals fed a carcinogenic diet of 3'-methyl-DAB showed inhibited DNA fixation at the beginning of the feeding experiment. Between the 20th and 30th day of the experimental feeding, DNA fixation was identical in all three groups of rats. Azoreductase activity was greatly inhibited in all three groups of rats, and this low activity persisted as long as the carcinogens were fed. It is believed that activation and azoreduction act independently of each other. The drop in azoreductase activity does not seem to be related to the carcinogenic effect of azocarcinogens.

- 2302 THE EFFECTS OF DIETARY ALTERATIONS ON 3-METHYL-4-METHYLAMINOAZOBENZENE N-DEMETHYLASE ACTIVITY. (E.) Billings, R. E. (U. Minnesota Med. Sch., Minneapolis) and L. W. Wattenberg. *Proc Soc Exp Biol Med* 139(3):865-867, 1972.

Liver and small-intestine mucosal 3-methyl-4-methyla-



minoazobenzene (3-MMAB) demethylase activity was determined by a fluorometric technique. Female Sprague-Dawley rats fed 20 mg 3-methylcholanthrene (MC) in sesame oil daily for four days showed increased activity of both liver and small-intestine mucosal 3-MMAB demethylase, the increase in the small intestine being 3.2 times greater than that in liver. The effects of dietary alteration on 3-MMAB demethylase activity were also determined. Feeding of a purified diet and starvation both produced a marked decrease in enzyme activity in the small intestine but not in liver, when compared with the corresponding activities in rats maintained on a normal Purina Rat Chow diet. These results indicated that an inducer (or inducers) in the Purina Rat Chow diet was responsible for most of the 3-MMAB demethylase activity of the small bowel.

2303 VASCULAR CHANGES ASSOCIATED WITH THE APPEARANCE OF EXPERIMENTALLY-INDUCED CHEEK POUCH CARCINOMA IN THE GOLDEN HAMSTER. (Fr.) Delarue, J. (Dept. Path. Anat. Paris, France), J. Mignot, J. Diebold, J. P. Camilleri and M. Reynes. *C R Soc Biol (Paris)* 165(5):1001-1003, 1971.

The cheek pouches of 400 adult hamsters were painted three times a week with a 0.5% solution of 9,10-dimethyl-1,2-benzanthracene (DMBA) in mineral oil. In 250 hamsters the changes induced were periodically photographed following intravascular injection of a fluorescent substance, and histological examinations were performed on biopsied material from 150 hamsters. Vascular changes characteristic of malignant transformation occurred in 30% of the animals between the 80th and 100th day after the first application of DMBA; they consisted of very small vascular dilations of an order of 100 to 200 microns. Histological examination showed the lining of malpighian corpuscles in the epithelium was thickened by an increase in the number of cell layers without manifest disorganization. More often epithelial changes were characterized by disorganization of cell layers, nuclear anomalies, and dyskeratosis. These changes are similar to those found in intraepithelial cancer *in situ*. Vascular changes consisted of distension of all or part of the capillary loop which was covered with tumescent endothelial cells in close contact with the epidermal crest. The changes described occur at a very early intraepithelial stage before the tumor becomes invasive. It is not possible to say whether these vascular changes precede or follow the development of the tumoral cell clone, but there seems to be a synergism between the two phenomena.

2304 MALIGNANT TRANSFORMATION OF CELLS DERIVED FROM MOUSE PROSTATE BY EPOXIDES AND OTHER DERIVATIVES OF POLYCYCLIC HYDROCARBONS. (E.) Marquardt, H. (McArdle Lab. Cancer Res., U. Wisconsin, Madison), T. Kuroki, E. Huberman, J. K. Selkirk, C. Heidelberger, P. L. Grover and P. Sims. *Cancer Res* 32(4):716-720, 1972.

The ability of benz(a)anthracene (BA), dibenz(a,h)anthracene (DBA) and 3-methylcholanthrene (MCA) and the ability of their K-region derivatives (*cis*- and *trans*-dihydrodiols, epoxides and phenols) to induce morphological transformation of G23 clone C3H mouse prostate cells *in vitro* was studied. MCA (1.5 and 10  $\mu$ g/ml) was weakly active in transforming G23 cells as determined by the number of piled-up cell foci per culture after 24 hr exposure. Non-piled-up areas of the same dish were used as controls. BA (1.0 and 5.0  $\mu$ g/ml) and DBA (1.0 and 10  $\mu$ g/ml), the K-region *cis*- and *trans*-dihydrodiols of BA, DBA and MCA, and the K-region phenols of BA and DBA were completely inactive. The phenol of MCA was moderately active. The K-region epoxides of BA, DBA, and MCA, however, were extremely active in producing transformation. Non-K-region epoxides, non-carcinogenic hydrocarbons and their K-region epoxides were inactive. The K-region epoxide of 7-methyl-BA was slightly less active than BA in inducing transformation. 7-Bromomethyl-BA and 7-bromomethyl-12-methyl-BA were almost inactive. DMBA (0.1, 1.5 and 10  $\mu$ g/ml) was very active in transforming G23 cells. The toxicity of all compounds varied directly with concentration, the K-region epoxides of BA and MCA being the most toxic. Transformed cells inoculated, s.c., in isologous C3H mice induced anaplastic soft-tissue sarcomas, whereas control cells did not give rise to any tumors.

2305 REDUCTION BY PITUITARY ISOGRAFT OF INHIBITORY EFFECT OF LARGE DOSE OF ESTROGEN ON INCIDENCE OF MAMMARY TUMORS INDUCED BY CARCINOGEN IN OVARECTOMIZED RATS. (E.) Nagasawa H. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan) and R. Yanai. *Int J Cancer* 8:463-467, 1971.

Experiments were performed to determine whether a supply of prolactin in excess of that secreted by the pituitary, induced by estradiol benzoate (EB), might overcome the inhibitory effect of a large amount of estrogen on mammary tumor growth, which in turn, might increase tumor incidence. Female Sprague-Dawley rats were bilaterally ovariectomized at 45 days of age and injected s.c. with 20  $\mu$ g EB each postoperative morning; at 52 days of age they were given i.v. injections of 5 mg 7,12-dimethylbenz(a)anthracene (DMBA). After two months they were separated into four groups: I, no pituitary grafting; II, grafted with three isologous pituitaries under the right kidney capsule; III and IV, each received six pituitaries. EB injections were given to all groups except IV, and discontinued after grafting. After an average latency period of 111 days incidence of mammary tumors was found to be higher for groups II (62%) and III (80%) than group I (35%). Three months after grafting serum prolactin levels were found to be significantly higher in groups II and III than in groups I and IV. On the basis of the results, it is concluded that pituitary grafting does reduce the inhibitory action of a large dose of estrogen on the growth of DMBA-induced mammary tumors of the rat and results in an increased incidence of the tumors.

- 2306 DIFFERENTIAL EFFECTS OF ESTROGEN AND PROLACTIN ON DNA SYNTHESIS IN ORGAN CULTURES OF DMBA-INDUCED RAT MAMMARY CARCINOMA. (E.) Welsch, C. W. (Dept. Anatomy, Michigan St. U., East Lansing) and E. M. Rivera. *Proc Soc Exp Biol Med* 139(2):623-626, 1972.

The ability of estrogen and prolactin to promote DNA synthesis in rat mammary cancers induced in female Sprague-Dawley rats by 7,12-dimethylbenzanthracene (DMBA) and maintained in organ cultures was compared. Estrogen-17 $\beta$  (0.0001-10.0  $\mu$ g/ml), prolactin (5.0  $\mu$ g/ml), or both, were added to organ cultures for five days.  $^3$ H-Thymidine was added four hr prior to termination of the experiment. Prolactin produced about a fourfold ( $p < 0.01$ ) stimulation of incorporation of  $^3$ H-thymidine into DNA, as compared to controls. At all levels, estrogen alone had no stimulatory effect on DNA synthesis. Estrogen and prolactin combined produced a three-fold stimulation ( $p < 0.01$ ) in  $^3$ H-thymidine incorporation, which was significantly ( $p < 0.05$ ) less than that produced by prolactin alone. Significant ( $p < 0.01$ ) inhibition of  $^3$ H-thymidine incorporation into DNA and significantly ( $p < 0.01$ ) reduced levels of total DNA were observed in cultures containing 5.0 or 10.0  $\mu$ g/ml of estrogen. The total lack of a stimulatory effect by estrogen *in vitro* on DNA synthesis of mammary carcinoma was consistent with the hypothesis that estrogens are mammary oncogenic agents primarily as a result of their ability to influence prolactin secretion.

- 2307 OVARIAN AND OTHER TUMOR INDUCTION BY 7,12-DIMETHYLBENZ(a)ANTHRACENE IN THE SYRIAN GOLDEN HAMSTER. (E.) Toth, B. (U. Nebraska Coll. Med., Omaha). *Tumori* 57(3):169-180, 1971.

Tumor induction was studied in Syrian golden hamsters given either two or three i.v. injections of 7,12-dimethylbenz(a)anthracene (DMBA) at weekly intervals. The higher dose reduced survival time to a greater extent than the lower dose. Of 28 females receiving two injections, 21 developed ovarian tumors following a latent period of 44 wk; eight were granulosa cell type, two were theca cell type and 11 were mixed (granulosa-theca) cell type. Of 28 females receiving three injections, 24 developed ovarian tumors; 15 were granulosa type, four were theca type and four were mixed. The average latent period was 38 wk. Dermal melanocytomas developed in 24 of 28 females and 19 of 28 males receiving two weekly injections, and in 21 of 28 females and 22 of 28 males receiving three weekly injections. The incidence of squamous cell papillomas and carcinomas of the stomach was increased in males and females of both groups. Breast tumors were observed in 11 out of 28 of the females receiving two injections and in 18 of 28 of the males receiving three injections. Three and four females from the two- and three-injection groups, resp., developed malignant lymphomas. It is concluded that DMBA may be used to induce ovarian tumors with high efficiency.

- 2308 DEPRESSION OF HOMOGRAFT REJECTION AND GRAFT-VERSUS-HOST REACTIVITY FOLLOWING

- 7,12-DIMETHYLBENZ(a)ANTHRACENE EXPOSURE IN THE RAT. (E.) Di Marco, A. T. (Inst. Gen. Path., U. Bologna, Italy), C. Franceschi, L. Xerri and G. Prodi. *Cancer Res* 31(10):1446-1450, 1971.

The early effects of carcinogenic doses of 7,12-dimethylbenz(a)anthracene (DMBA) on cellular immunity in the rat are studied with the use of skin grafts performed across a weak histoincompatibility and graft-*versus*-host assays. Skin graft experiments were performed on three-month-old F344 and Lewis female inbred rats as donors and hosts, resp. DMBA was injected i.p. into hosts at a total dosage of 50  $\mu$ g/g body weight, 19  $\mu$ g on the first and fifth days and 12  $\mu$ g on the eighth day. All controls were given i.p. injections of olive oil. Rats were grafted from 10 to 13 days after treatment was begun; controls were grafted on the fifth day. Graft-*versus*-host assays were performed five or six days after i.p. injection of a single 50  $\mu$ g/g body weight dose of DMBA into donor F344 rats. DMBA treatment significantly prolonged the survival time of grafts performed 10 to 13 days following DMBA exposure and also delayed the appearance of the earliest signs of rejection. However, homografts performed five days after the beginning of DMBA treatment were rejected after an ordinary first-set reaction. The reactivity of spleen cells from control and DMBA-treated F344 rats against a strong (AgB) histocompatibility barrier was investigated. Doses of 2.5, 5, and 10  $\times 10^6$  cells from 4 to 5 pooled spleens were injected into F344  $\times$  B6F<sub>1</sub> newborn rats. Treated cells were less than one-half as reactive as controls. The spleen cell reactivity of both normal and treated F344 rats was tested against a weak histoincompatibility by injecting doses of 20 and 40  $\times 10^6$  cells into F344  $\times$  Lewis F<sub>1</sub> newborn rats. While a weak reaction was obtained with the largest control dose, the treated cells were always unreactive. Further graft-*versus*-host assays with cells from the donor sensitized against the hybrid partner were performed in order to investigate the mechanism of cell-mediated immunity damage. There was no difference in sensitization lowering of DMBA-treated animals whether the carcinogen was given before or after sensitization. This suggests that lymphocytic damage occurs in cell-mediated immunity depression, while this type of immunity does not show the early, remarkable damage characterizing the humoral process.

- 2309 MAMMARY NEOPLASTIC RESPONSE OF LEWIS AND SPRAGUE-DAWLEY FEMALE RATS TO 7,12-DIMETHYLBENZ(a)ANTHRACENE OR X-RAY. (E.) Shellabarger, C. J. (Med. Dept., Brookhaven Natl. Lab., Upton, N.Y.). *Cancer Res* 32(5):883-885, 1972.

Weanling female Lewis or Sprague-Dawley rats were given either 13.3 mg of 7,12-dimethylbenz(a)anthracene (DMBA) per 100 g body wt. by stomach tube, or total body X-radiation (350 R at 250 kVp) on the 50th day of age. Controls were untreated. All rats were examined frequently for ten months for palpable mammary tumors which were removed surgically when they reached a size of three cm. At the end of the ten months, all rats were killed and examined for tumors. Twenty of 29 Lewis rats given DMBA developed mammary neoplasia, including 43 mammary adenocar-



cinomas and one mammary fibroadenoma, while 24 of 29 Sprague-Dawley rats given DMBA developed mammary neoplasia, including 39 adenocarcinomas and 53 fibroadenomas. Six of 40 Lewis rats given X-radiation developed mammary neoplasia, including four mammary adenocarcinomas and four mammary fibroadenomas, while of 40 Sprague-Dawley rats given X-radiation, 26 developed mammary neoplasia including 11 adenocarcinomas and 39 fibroadenomas. None of 22 nontreated Lewis rats developed mammary neoplasms, while three of 44 nontreated Sprague-Dawley rats developed mammary neoplasms, including one mammary adenocarcinoma and two fibroadenomas. It is concluded that DMBA is a somewhat more potent carcinogen than X-radiation in both strains. Although the mammary adenocarcinoma response to either DMBA or X-radiation was similar in both strains, a relative lack of a mammary fibroadenoma response in Lewis rats was noted, compared to that in Sprague-Dawley females. This new finding is unexplained.

2310 RECURRENCES OF 7,12-DIMETHYLBENZ(a)ANTHRA-CENE-INDUCED MAMMARY TUMOR IN RATS AFTER ITS SURGICAL EXTIRPATION. (E.) Imaizumi, T. (Jikei U. Sch. Med., Japan) and I. Ohira. *Jikei Med J* 18: 7-10, 1971.

A study of tumor recurrence in virgin female Sprague-Dawley rats after surgical extirpation of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors is presented. The six-wk-old 150 g animals were given a single intragastric feeding of 10 mg DMBA in 1 ml olive oil. After 200 days 15 of 16 rats developed mammary tumors, mostly adenocarcinomas. Eight rats underwent surgical extirpation of their tumors while eight others received no treatment. Tumors were found to recur in the same sites as the original in some cases and in different sites in others. Recurrence of tumors in the same site indicated that part of the tumor remained for infiltration. Recurrence in a different site may be explained by: 1) development of already existing tumors or 2) *de novo* tumor development in mammary tissue.

2311 METABOLISM OF POLYCYCLIC HYDROCARBONS IN MAMMALIAN CELL CULTURES. (E.) Diamond, J. (Wistar Inst. Anatomy Biol., Philadelphia, Pa.). *Int J Cancer* 8:451-462, 1971.

Culture conditions which influence the metabolism of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) to polar derivatives were studied using two extraction procedures to measure metabolism. Metabolism of the hydrocarbons to "alkali-extractable derivatives" was measured by extraction of labeled medium with acetone:hexane, followed by extraction of the resulting acetone-hexane phase with NaOH (extraction procedure I). Metabolism to "water-soluble derivatives" was measured by extraction of the medium with chloroform:methanol:water (extraction procedure II). Low passage and established lines of rodent and primate cells were treated with BP or DMBA, and hydrocarbon metabolism was measured. The

relationship between carcinogen-induced cytotoxicity and hydrocarbon metabolism was examined. In extraction procedure I, rodent cells showed intermediate to high levels of conversion of BP and DMBA to water-soluble derivatives, while primate cells (with the exception of fetal human lung cells) showed low levels of conversion. In general, hydrocarbons were metabolized most efficiently to water-soluble derivatives by cells which were sensitive to the growth-inhibitory effects of BP and/or DMBA, while little metabolism occurred in cells resistant to the toxic effects of these agents. Hydrocarbon metabolism to water-soluble derivatives depended on carcinogen concentration and on density of the cell monolayer. In extraction procedure II, the amount of alkali-extractable derivative of BP recovered from the medium with hamster cells decreased after nine hr of incubation, while the amount of water-soluble product continued to increase. Data on kinetics of metabolism of BP and DMBA suggested that there may be a sequential conversion of BP first to alkali-extractable and then to water-soluble metabolites.

2312 RESPIRATORY TRACT CARCINOGENESIS IN HAMSTERS INDUCED BY DIFFERENT NUMBERS OF ADMINISTRATIONS OF BENZO(a)PYRENE AND FERRIC OXIDE. (E.) Saffiotti, U. (Nat'l. Cancer Inst., Bethesda, Md.), R. Montesano, A. R. Sellakumar, F. Cefis and D. G. Kaufman. *Cancer Res* 32(5):1073-1081, 1972.

Administration of varying amounts of benzo(a)pyrene (BP) and ferric oxide was found to induce respiratory tract tumors in Syrian golden hamsters of both sexes. Four groups of seven- to 11-wk-old hamsters received a single intratracheal instillation in 0.5 ml of 0.9% saline in the following doses: Group 1, 37.5 mg BP and 12.5 mg ferric oxide; Group 2, 5 mg BP and 45 mg ferric oxide; Group 3, 50 mg ferric oxide; Group 4, saline alone. Six groups of eight- to 11-wk-old hamsters received multiple doses of 3 mg BP and 3 mg ferric oxide in 0.2 ml 0.9% saline with the following amounts: Groups 5 and 6, 15 weekly doses; Groups 7 and 8, 10 weekly doses; Group 9, 5 weekly doses; Group 10, 5 doses given every 25 days. Of the 61 animals in Group 1, five developed bronchogenic carcinomas, and five, histologically benign respiratory tumors. Of the 61 hamsters in Group 2, one developed a bronchiolar-alveolar adenocarcinoma at 79 wks; and six others developed histologically benign respiratory tumors. No respiratory tumors were found in Groups 3 and 4. Groups 5 through 10 showed clear dose-response pattern as indicated by an increase in latency period for respiratory tumors with decreasing number of administrations. In these groups, squamous cell tumors were found induced most often in the bronchi and trachea. Results indicate that even one respiratory exposure to carcinogenic polynuclear hydrocarbon is enough to produce bronchogenic carcinoma.

2313 EFFECTS OF BENZO(a)PYRENE ON ISOLATED RAT LIVER MITOCHONDRIA. (E.) Cuccurullo, L.

(Dept. Path., U. Naples, Italy) and G. Manocchio. *Experientia* 28(3):311-312, 1972.

Purified rat liver mitochondria were incubated in an aqueous solution of 2% benzo(a)pyrene for 30 min, then fixed in phosphate-buffered glutaraldehyde and post-fixed in osmium tetroxide for electron microscopic examination. The mitochondria were seen to be increased in volume, have a rounded shape and contain a pale and homogeneous matrix. Cristae were rare and those observed were broken. Intracrystal spaces were vastly reduced in size. Mitochondrial swelling, which resulted in rupture of the surface membrane and extrusion of the contents, was brought about at the expense of the "cytoplasmic" compartment (mannitol-impermeable) and was possibly preceded by benzo(a)pyrene-induced alterations of the internal membrane.

2314 INTERACTIONS OF BENZOPYRENE AND STEROID HORMONES WITH ISOLATED RAT LIVER MITOCHONDRIA. (E.) Santamaria, L. (C. Golgi Inst. Gen. Path., U. Pavia, Italy) and E. Calenei. *Boll Chim Farm* 110(7):368-376, 1971.

Twelve steroid hormones were tested for their ability to induce swelling in isolated rat liver mitochondria suspended in 0.5 M sucrose and exposed to light ( $\lambda > 320$  nm). Compounds were classified as having a primary or secondary effect, depending upon whether mitochondrial swelling was induced during or after exposure to light. Testosterone, deoxycorticosterone, progesterone, androstosterone, and androsterone showed strong secondary effects; the effect of estradiol was negligible. When EDTA was used instead of tris buffer, benzo(a)pyrene (BP) still showed a primary effect, whereas epianthrosterone, etiocholanone and dehydroepianthrosterone showed no effect. Dehydrocorticosterone showed a slight secondary effect in another experiment. Of all the steroids tested, only testosterone caused mitochondrial swelling in the dark. The primary effect of BP was shown to depend initially upon the presence of oxygen. Secondary effects required the presence of oxygen throughout the entire swelling period. Estradiol and estradiol decreased the primary effect of BP, and it was concluded that they competed with BP for the same sites on the mitochondria.

2315 PRODUCTION OF ALTERED CELL FOCI BY 3-METHYLCHOLANTHRENE IN MOUSE CELLS INFECTED WITH AKR LEUKEMIA VIRUS. (E.) Rhim, J. S. (Nat. Cancer Inst., Bethesda, Md.), B. Creasy and R. J. Huebner. *Proc Nat Acad Sci USA* 68(9):2212-2216, 1971.

NIH Swiss mouse embryo cells, infected with AKR leukemia virus, were plated in a medium which was replaced after one day with a medium containing 0.5 or 0.1  $\mu\text{g/ml}$  of 3-methylcholanthrene (MCA). MCA treatment was performed for seven days. Some MCA-treated cells had not been virus-infected, and some virus-infected cells had not been MCA-treated, while other cells had received neither treatment (three control groups). Twelve days after MCA treatment, foci of

piled-up cells, randomly oriented, were found in virus-infected cultures, but not in MCA-treated but uninfected cells. Infected cells not treated with MCA were also normal. Changes were first seen in virus-infected cells treated with 0.5  $\mu\text{g/ml}$  MCA. Transformed foci were made up of spindle-shaped cells showing loss of contact inhibition. It was speculated that infectious but non-transforming RNA tumor viruses (e.g., AKR leukemia virus) may provide nascent oncogenic information which, activated by MCA, serves as the specific genetic determinant of cell transformation.

2316 PRODUCTION OF VARIANTS OF DECREASED MALIGNANCY AND ANTIGENICITY FROM CLONES TRANSFORMED *IN VITRO* BY METHYLCHOLANTHRENE. (E.) Mondal, S. (McArdle Lab. Cancer Res., U. Wisconsin, Madison), M. J. Embleton, H. Marquardt and C. Heidelberger. *Int J Cancer* 8:410-420, 1971.

Variant clones were derived from a highly malignant line of C3H mouse prostate cells treated *in vitro* with 3-methylcholanthrene (4C<sub>1</sub> cells). For cloning, 4C<sub>1</sub> cells were plated on glutaraldehyde-fixed C3H embryo cells or treated with 5-fluoro-2'-deoxyuridine (FUDR). Saturation densities of cells from non-transformed cells and of variants derived from transformed clones ranged from 0.43-0.75 cells/cm<sup>2</sup>  $\times 10^5$ . The highly malignant 4C<sub>1</sub> clone had a density of 1.3 cells/cm<sup>2</sup>  $\times 10^5$ . Treatment of 4C<sub>1</sub> clone cells by plating on glutaraldehyde or FUDR treatment produced variant clones of greatly reduced malignancy. 4C<sub>1</sub> cells produced tumors in isologous mice when  $5 \times 10^4$  cells were injected, whereas cells of the variant clones usually required inocula of  $10^5$ - $10^6$  cells to produce tumors. Loss of malignancy in clones was accompanied by gain and loss of chromosomes. The chromosomal mode of 4C<sub>1</sub> cells was 56, while the less malignant FUDR-treated variants had modes of 48-49 and the less malignant glutaraldehyde-plated variants had modes of 95-96. In complement-inhibition tests, it was found that the 4C<sub>1</sub> cells possessed cell-surface antigens capable of inducing humoral and cell-mediated immune responses in C3H mice. The less malignant variants were deficient in the 4C<sub>1</sub> antigen, though their cell-surface alloantigens were unchanged.

2317 EFFECT OF 3-METHYLCHOLANTHRENE AND FISSION NEUTRON IRRADIATION, GIVEN SINGLY OR COMBINED, ON RAT MAMMARY CARCINOGENESIS. (E.) Shellabarger, C. J. (Brookhaven Natl. Lab., Upton, New York) and R. F. Straub. *J Nat Cancer Inst* 48(1):185-187, 1972.

Female Sprague-Dawley rats were given a single, oral 40-mg dose of 3-methylcholanthrene (MCA) on the 42nd day of age, or 100 rads of total-body fission neutron radiation on the 52nd day, or both, or the sequence of administration of the two carcinogenic agents was reversed. All animals survived until they were sacrificed at 142 days of age. No mammary tumors developed in the 21 untreated controls. Seven of 38 rats exposed to



neutrons at 42 days developed nine histologically diagnosed mammary adenocarcinomas and seven of 38 rats treated with neutrons on day 52 developed eight mammary adenocarcinoma. Treatment with MCA alone produced a slightly greater response with mammary adenocarcinoma (23 tumors in 14 of 38 rats treated on day 42 and 15 tumors in 15 of 38 rats treated on day 52). Combination of MCA and neutron irradiation given to the same animals, regardless of the sequence of administration of the two carcinogens, produced an adenocarcinoma response which approximated the sum of the responses of each carcinogen given alone (49 tumors in 38 of 76 rats). Fission neutron irradiation, either alone or combined with MCA, produced decreases in both body and ovarian weights whereas, MCA alone had no significant effect on either. The number of mammary fibroadenomas induced by the two carcinogens was insufficient to draw any conclusions concerning these tumors.

- 2318 INFLUENCE OF GENETIC FACTORS ON THE INDUCTION OF MAMMARY AND INTESTINAL ADENOCARCINOMAS IN INBRED SYRIAN GOLDEN HAMSTERS. (E.) Homburger, F. (Bio-Res. Inst., Cambridge, Massachusetts), C. S. Kerr and S.-S. Hsueh. *Nature New Biol* 234(44):28-29, 1971.

The inherited susceptibility or resistance of seven inbred male and female Syrian golden hamster lines to the development of intestinal and/or mammary adenocarcinoma was studied after administration by stomach tube of 3-methylcholanthrene (MC) three times weekly for 17 wk. Autopsies were performed between four and 30 wk thereafter. None of the control animals developed mammary or intestinal adenocarcinomas. Most animals fed MC had benign papillomas of the forestomach. A significant number of invasive stomach adenocarcinomas were seen only in males of the 87.20 line. Small intestinal adenocarcinomas occurred in males and females in half the animals of line 4.22 and in half of the 87.20 male, but in only 12% of the 87.20 females. Almost no large intestinal tumors were seen in the 4.22 line, but 87.20 males had 65% and 87.20 females, 33%. Fifty percent of males of line 15.16 had large intestinal tumors. There was no significant incidence of tumors of the male reproductive tract. Two inbred lines (RB and 86.93) with a low incidence of intestinal tumors had 50% ovarian tumors. Only one line (54.7) with a low intestinal tumor incidence had a significant (42%) incidence of uterine tumors. Susceptibility to mammary tumor induction by MC in females reached 80-90% in five lines (15.16, 54.7, 82.73, 86.93, and 87.20) and 52 and 61% in RB and 4.22 lines, respectively.

- 2319 CARCINOGENIC NITROSAMINES IN CANTONESE SALT-DRIED FISH. (E.) Fong, Y. Y. (U. Hong Kong, Hong Kong) and E. O'F. Walsh. *Lancet* (7732): 1032, 1971.

Cantonese salt-dried fish were examined for the presence of nitrosamines by gas-liquid chromatography

in an attempt to provide an etiologic explanation for the high incidence of nasopharyngeal carcinoma in the Hong Kong region. All nine species of fish examined, including salt-dried anchovies, croakers, yellow croakers and white herrings, contained dimethylnitrosamine (0.6-9.0 ppm) and diethylnitrosamine (1.2-21.0 ppm). Viable cultures of nitrate-reducing halobacteria and salt-tolerant *Staphylococcus aureus* have been isolated from all the samples of fish examined.

- 2320 NITROSAMINE-INDUCED CARCINOGENESIS: THE ALKYLATION OF N-7 OF GUANINE OF NUCLEIC ACIDS OF THE RAT BY DIETHYLNITROSAMINE, N-ETHYL-N-NITROSOUREA AND ETHYL METHANESULPHONATE. (E.) Swann, P. F. (Middlesex Hosp. Med. Sch., London, England) and P. N. Magee. *Biochem J* 125(3):841-847, 1971.

Wistar-derived albino rats of both sexes were given <sup>14</sup>C-labeled diethylnitrosamine (250 mg/kg injected i.p.), <sup>14</sup>C-labeled ethyl methanesulphonate (270 mg/kg injected i.p.), or <sup>14</sup>C-labeled N-ethyl-N-nitrosoarea (150 mg/kg injected i.v.). Rats were killed 1.5-24 hr postinjection and nucleic acids were prepared from liver, kidney, lung, intestine and brain. Nucleic acids were hydrolyzed and chromatographed on a Dowex 50W column (10 cm x 1 cm). The incidence of kidney tumors produced in rats by the three compounds was compared with the amount of ethylation by the three compounds. A single dose of diethylnitrosamine or N-ethyl-N-nitrosoarea produced kidney tumors in the rats. Three 270 mg/kg doses of ethyl methanesulphonate produced kidney tumors but a single 350 mg/kg dose did not. All three compounds produced measurable amounts of 7-ethylguanine. A single dose of 270 mg/kg ethyl methanesulphonate produced five times more 7-ethylguanine in rat kidney DNA than the carcinogenic dose of diethylnitrosamine, and ten times more than the carcinogenic dose of N-ethyl-N-nitrosoarea. Tumors induced by the three compounds were not all the same histological type. It was not clear whether the production of tumors with diethylnitrosamine (epithelial tumors) and with ethyl methanesulphonate or N-ethyl-N-nitrosoarea (mesenchymal tumors) represented a real difference in the action of these chemicals.

- 2321 FORMATION OF N-NITROSODIMETHYLAMINE FROM NATURALLY OCCURRING QUATERNARY AMMONIUM COMPOUNDS AND TERTIARY AMINES. (E.) Fiddler, W. (US Dept. Agric., Philadelphia, Pa.), J. W. Pensabene, R. C. Doerr and A. E. Wasserman. *Nature* 236(5345): 307, 1972.

A report on the formation of dimethylnitrosamine (DMNA) from several quaternary ammonium compounds and some of their related tertiary amines under conditions simulating those found in comminuted meat products is presented. The N-containing compounds were reacted with NaNO<sub>2</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub> and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>; DMNA determination was done by GLC. It was found that DMNA

was formed from tetramethylammonium chloride at almost the same level as from trimethylamine. DMNA was also produced by the naturally occurring quaternary ammonium compounds, neurine, carnitine, betaine, choline and acetylcholine, when reacted with  $\text{NaNO}_2$ ; however, much less DMNA was formed than from the tetramethylammonium compound. The yield of DMNA from the mixed alkyl tertiary amines was two to five times more than from trimethylamine and  $4\text{--}20 \times 10^3$  times more than from the quaternary ammonium compounds. It is concluded that the tertiary and free secondary amines in food products are of greater concern as a source of DMNA than quaternary ammonium compounds.

- 2322 METHYLATION OF NUCLEAR AND CYTOPLASMIC RNA OF MOUSE LIVER WITH DIMETHYLNITROSAMINE- $^3\text{H}$ . (E.) Muramatsu, M. (Cancer Inst., Tokyo, Japan), Y. Azama, N. Nemoto and S. Takayama. *Cancer Res* 32(4):702-709, 1972.

The labeling patterns of methylation of nuclear and cytoplasmic RNA in mouse liver were examined at various times after i.p. administration of tritiated dimethylnitrosamine (DMN- $^3\text{H}$ ). Sucrose gradient centrifugation analysis showed that 28S and 18S RNA, 4S and 5S RNA, nuclear ribosomal and low molecular-wt (4 to 7S) RNA, and possibly rapidly labeled rRNA, were rapidly methylated by DMN. The average specific activity of rRNA was almost the same as that of cytoplasmic RNA at 10 and 30 minutes after injection, indicating the rapid penetration and reaction of DMN with rRNA's. The degree of methylation, however, was different with RNA species; the ratio of the number of methyl groups that were introduced per unit nucleotide length was 1.3:1.0:1.6 for 28S, 18S and 4S RNA, resp., at five different times studied. Paper chromatographic analysis of  $^3\text{H}$ -labeled cytoplasmic RNA hydrolysates showed that almost all radioactivity was associated with  $\text{N}^7$ -methylguanine. Methylation of the position 2' O of ribose moiety was not detected. Methylated RNA became unstable *in vivo*. A fraction of rRNA that had been methylated by DMN degraded with a half-life of approximately 1.5 days. RNA which was less extensively methylated decayed with a half-life of three to four days while normal rRNA had a half-life of five days.

- 2323 EFFECTS OF FEEDING THE CARCINOGEN DIMETHYLNITROSAMINE ON ITS METABOLISM AND METHYLATION OF DNA IN THE MOUSE. (E.) Engelse, L. D. (Netherlands Cancer Inst., Amsterdam) and P. Emmelot. *Chem-Biol Interactions* 4(5):321-327, 1972.

Male inbred C3H<sub>f</sub> mice having a high incidence of spontaneous liver tumors were pretreated for six wk by the addition of ten ppm dimethylnitrosamine (DMNA) to their drinking water. At 0, 6, 10 and 17 wk after the start of the experiment, one injection of  $^{14}\text{C}$ -DMNA (7 mg/kg body wt, i.p.) was given, and 48 hr later the 7-methylguanine (7-MeG) contents of purified lung, liver and kidney DNA were determined. The 7-MeG content of liver DNA decreased by 50% and

that of lung and kidney DNA increased by 80 and 100%, resp. following pretreatment with DMNA. The methylation patterns were reversible, since normal or near-normal 7-MeG levels were obtained when 4-11 wk had elapsed between pretreatment with DMNA and injection of  $^{14}\text{C}$ -DMNA. Pretreatment with DMNA inhibited by 80% the DMNA-N-demethylating enzyme activity of liver microsomes. This inhibition was reversible when DMNA was removed from the drinking water. Blood DNA levels determined by gas chromatography 60 and 120 min after injection of DMNA were 25 to 100% higher in pretreated than in control animals. It is concluded that the liver-N-demethylating enzyme activity governs both the rate of methylation of liver DNA, and the amount of systemic DMNA available for metabolic demethylation and DNA methylation in lung and kidney.

- 2324 INDUCTION OF LIVER TUMORS IN THE AQUARIUM FISH, *LEBISTES RETICULATUS* (GUPPIES), WITH NITROSAMINES. (Rus.) Khudolei, V. V. (N. I. Petrov Sci. Res. Inst. Oncology, Ministry Public Hlth. USSR, Leningrad). *Vop Onkol* 17(12):67-72, 1971.

When guppies were kept in aquaria containing 26-100 ppm diethylnitrosamine (DENA) or 100 ppm dimethylnitrosamine (DMNA) for 10-64 days, about 25% of the fish developed liver tumors. Poorly differentiated hepatocellular cancer, which was multicentric and grew invasively, was associated in some cases with fatty dystrophy of the liver; none of these liver tumors metastasized. In addition to these malignant tumors, benign multicentric hepatic adenomas, proliferation of biliary tract epithelium, and benign cholangiomas were also observed. Between 20 and 68% of the guppies died during these experiments; females appeared to be more resistant to the toxic effects of DENA and DMNA than males. Although no quantitative measurements were made of the amount of carcinogens actually absorbed by the fish, it appears that guppies are extremely sensitive to the carcinogenic action of nitrosamines and might be suitable for use in cancer experiments.

- 2325 MUTAGENICITY OF DIMETHYLNITROSAMINE AND DIETHYLNITROSAMINE FOR *SACCHAROMYCES* IN AN *IN VITRO* HYDROXYLATION SYSTEM. (E.) Mayer, V. W. (Food Drug Admin., Washington, D. C.). *Molec Gen Genet* 112(4):289-294, 1971.

Two potent carcinogens, dimethylnitrosamine (DMN) and diethylnitrosamine (DEN) and homologous secondary amines dimethylamine (DMA) and diethylamine (DEA), which lack the nitroso group of DMN and DEN, were tested for their ability to induce petite and canavanine-resistant mutants in the wild-type haploid strain, D273-10B, of *Saccharomyces cerevisiae*. DMN, DEN, and DEA were added to separate reaction mixtures of Udenfriend's hydroxylation medium and oxygen was passed through the liquid. Control reaction mixtures had nitrogen bubbled through them. *S. cerevisiae* cells were added to each of the experimental reaction



mixtures and incubated at 30°C. Samples of treated cells to be tested for the incidence of petite mutants were removed from the reaction mixtures at hourly intervals, plated onto agar and observed after 48 hr. Samples tested for canavanine-resistant mutants were removed after six hr and placed on canavanine minimal medium. Petite mutants were induced by DMN and DEN in the presence of oxygen but not in the presence of nitrogen. The mutant frequency increased with the time the cells were exposed to the carcinogen. After five hr exposure, the incidence of petite mutants was 98.6% of the DMN-treated population and nearly 45% of the DEN-treated population; DMA and DEA did not induce petite mutants. A similar pattern of canavanine-resistant mutant induction by DMN and DEN, but not by DMA or DEA, was seen. The results indicate that the nitroso group is necessary for the mutagenic activity. Moreover, since the mutational effects of DMN and DEN occurred only with oxygen and it is known that breakdown occurs with oxygen, these results indicate that the parent compounds were inactive, but some breakdown products of DMN and DEN were the genetically active entities.

- 2326 DEMONSTRATION OF CELLULAR IMMUNITY AGAINST URETHAN-INDUCED LUNG ADENOMAS OF MICE. (E.) Colnaghi, M. I. (Natl. Inst. Stud. Care Tumors, Milan, Italy), S. Menard and G. D. Porta. *J Nat Cancer Inst* 47(6):1325-1331, 1971.

Immunologic responses to urethan-induced lung adenomas in ten-day-old SWR/DeDp inbred mice were studied *in vitro* with a microassay for cell-mediated cytotoxicity. The first group of mice was given i.p. injections of urethan (U) (0.2 mg/g body wt) once every second day for ten days. Two other groups were given the same U treatment as well as five injections on alternate days of either 0.01 mg cyclophosphamide (CP) or 0.1 mg cortisone (C)/g body weight. Mouse adenomas were pooled; the resulting cell suspension was seeded in tissue culture microplates and also used for s.c. injection of  $1-2 \times 10^6$  viable cells into SWR mice. Direct tests using immune lymphoid cells which had been tested on the same adenoma cell preparations as those used for immunization gave positive results for five of the six tumors from mice given U plus C or CP; the three tumors from mice given only U were negative. Cross-reaction tests gave positive results for nine of 13 tumors using both immunizing target cells from U-plus C-, or CP-, treated mice; negative results (four cases) were obtained when the immunizing pulmonary adenomas were from mice given U alone and the target cells were from tumors of mice given C and CP. S.c. nodules appeared in  $13.2 \pm 1.9$  days in mice injected with lung adenoma pools from animals given U alone; nodules were seen in  $27.9 \pm 1.2$  days and  $26.1 \pm 4.3$  days in mice given tumor pools from mice injected with U plus C and U plus CP, resp. These results show that urethan-induced lung adenomas had a cross-reacting antigenicity detectable *in vitro* that depended on the immunological status of the tumor donors, suggesting an immunoselective process in the animals not receiving the immunodepressive drugs.

- 2327 ULTRASTRUCTURAL STUDY OF NUCLEOLAR ALTERATIONS PRODUCED BY A SINGLE CARCINOGENIC DOSE OF URETHAN IN MOUSE HEPATOCYTES. (E.) Lombardi, L. (Natl. Inst. Study Cure Tumors, Milan, Italy). *Cancer Res* 32(4):675-679, 1972.

A single i.p. injection of 1 mg urethan per mg body wt was given to seven- and 21-day-old C3Hf/Dp mice of both sexes. This treatment had previously been shown to induce hepatomas in 60% of females and 95% of males treated at the age of seven days and in 5% of females and 65% of males treated at 21 days of age. The sequence of ultrastructural nucleolar alterations in hepatic cells was studied by electron microscopy. Liver sections of seven- and 21-day-old and 20-wk-old untreated mice were examined as controls. In seven-day-old treated animals, "microspherules" ("electron-dense nodules" or "plaques") were found either within the meshes of the nucleolar network or at the periphery of the nucleolus, four and 12 hr after dosing. At 24 hr segregation of granular and fibrillar nucleolar components (nucleolar capping) was seen. By 72 hr, normal nucleolar structure was restored. Twenty wk later, hyperplastic nodules were macroscopically evident in livers. In both normal and hyperplastic tissue, disaggregation of nucleolus-associated chromatin and, more rarely, ring-shaped nucleoli were observed. Mice treated at 21 days did not develop nucleolar lesions but disaggregation of the nucleolus-associated chromatin, similar to that observed in the seven-day-treated animals, was seen at all observation times after urethan injection.

- 2328 ADDITIVE LEUKEMOGENICITY OF URETHAN AND X-IRRADIATION IN INFANT AND YOUNG ADULT MICE. (E.) Vesselinovitch, S. D. (Argonne Cancer Res. Hosp., U. Chicago, Ill.), E. L. Simmons, N. Mihailovich, L. S. Lombard and K. V. N. Rao. *Cancer Res* 32(2):222-225, 1972.

An experiment to evaluate urethan and X-irradiation in leukemogenesis is reported. Female C57BL x C3H F<sub>1</sub> infant mice were treated with 0.5 mg/g body wt. of urethan (ethyl carbamate) i.p. on the third, sixth and 12th day of life. Other infant female mice received fractional doses of X-radiation (total of 480r) on days zero, seven, 14 and 21. Other groups of mice received no treatment as infants but were treated with either urethan (days 42, 45, 51) or X-radiation (days 42, 49, 56, 63). All survivors were sacrificed and necropsied after the 56th wk. One group of mice served as nontreated controls. Exposure of infant mice to urethan resulted in development of leukemia in three of 49 (6.1%) of the animals with a mean duration until onset of tumors of  $31.6 \pm 11.7$  wk. None of 58 adult mice treated with urethan developed leukemia. Statistical analysis of the groups of mice treated with urethan or urethan plus X-radiation, as either infants or adults, revealed an additive leukemogenic effect between the two carcinogens. The incidence of leukemia in animals treated with X-radiation alone was 26.9% in infants and 40.8% in adults; the difference was not significant. Pre-treatment of infants with urethan followed by X-radiation of the same mice as adults produced leu-

kemia in 36 of 54 (66.7%) of the treated mice. When mice were treated with X-radiation as infants and urethan as adults, the tumor incidence was only 19 of 50 (38.0%), which was significantly lower ( $P < 0.01$ ) than the opposite treatment. This difference was attributed to lower susceptibility of the adult mice to the leukemogens. Pretreatment with urethan of mice receiving either one dose of X-radiation (320r) at age 42 days, or four exposures to 80r at weekly intervals, significantly increased ( $P < 0.02$ ) the tumor incidence (22.6 and 22.2% resp.) over that of mice receiving X-radiation at these doses only (2.5 and 10.9%, respectively). The average duration between treatment and onset of leukemia in the various groups was consistent with the idea that inception of the process took place at the first treatment, regardless of which leukemogen was used.

- 2329 THE REACTION OF URETHANE WITH MOUSE LIVER NUCLEIC ACIDS *IN VIVO*. (E.) Lawson, T. A. (Dept. Path., U. Queensland, Australia) and A. W. Pound. *Pathology* 3(3):223-225, 1971.

In a brief report the effect of urethane on mouse liver nucleic acids *in vivo* is discussed. Male adult Crackenbush mice were injected i.p. with urethane (ethyl-2-<sup>3</sup>H) 100  $\mu$ C/mouse and <sup>3</sup>H<sub>2</sub>O 100  $\mu$ C/mouse. Phenol extraction of DNA and RNA from sacrificed mouse livers was performed and the nucleic acids subjected to acid and enzyme hydrolyses. The hydrolysates were analyzed by paper chromatography; the DNA acid hydrolysates showed a radioactive spot separate from the major bases and nucleotides. Radioactivity of the hydrolysates was measured; it was found that urethane or a metabolite was bound to the mouse liver DNA and protein but not to the RNA.

- 2330 SUPPRESSION OF URETHAN-INDUCED LUNG ADENOMAS IN MICE TREATED WITH TREHALOSE-6,6-DIMYCOLATE (CORD FACTOR) AND LIVING BACILLUS CALMETTE-GUERIN. (E.) Bekierkunst, A. (Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel), I. S. Levij, E. Yarkoni, E. Vilkas and E. Lederer. *Science* 174(4015):1240-1242, 1971.

Albino mice were treated with i.v. injections of living bacillus Calmette-Guerin (BCG), cord factor (trehalose-6,6-dimycolate, a glycolipid from *Mycobacterium kansasii*), wax D (from *M. tuberculosis*) or a combination of cord factor and wax D. All mice received i.p. injections of urethan 17 days later. Two days after the injection of urethan, animals which had received cord factor and/or wax D were similarly injected with cord factor, wax D, or a mixture of both resp. Animals were killed 7 weeks after the urethan was injected. The presence of tumors in the lungs and cellular response were evaluated microscopically. Granulomas composed of epithelioid cells, macrophages, and lymphoid cells were present in all lungs of mice treated with BCG, cord factor or cord factor plus wax D. There was a significant suppres-

sion of urethan-induced tumors in the groups treated with BCG, cord factor, or a mixture of cord factor and wax D. Wax D alone did not affect the development of tumors, but in combination with cord factor it seemed to add to the effect exerted by the cord factor. It is concluded that the suppressed development of urethan induced tumors is due to the host cellular reaction caused locally by cord factor.

- 2331 THE EFFECT OF SOME POLYCYCLIC HYDROCARBONS AND TOBACCO CONDENSATES ON NONSPECIFIC ESTERASE ACTIVITY IN SEBACEOUS GLANDS OF MOUSE SKIN. (E.) Healey, P. (Huntingdon Res. Ctr., England), L. E. Mawdesley-Thomas and D. H. Barry. *J Pathol* 105(2):147-152, 1971.

The sebaceous gland suppression test for carcinogenic activity of polycyclic hydrocarbons has been modified to enable the enzymatic activity of the gland to be estimated with an image analyzing computer. All test substances used caused a reduction in the areas covered by enzyme activity associated with sebaceous glands, the maximum effect being obtained with those compounds known to be highly carcinogenic and the minimum effect with those compounds of doubtful carcinogenic activity. In a second experiment 250  $\mu$ g of dimethylbenzanthracene caused less suppression than the highest dose of the most potent tobacco condensate. Further, all the condensates were ranked in dose order. It is believed that this test may be of value in screening potentially carcinogenic condensates or fractions prior to more comprehensive testing.

- 2332 EFFECT OF CIGARETTE TAR UPON TISSUE CULTURE CELLS: NEOPLASTIC TRANSFORMATION OF HAMSTER LUNG CELLS BY TOBACCO TAR IN TISSUE CULTURE. (E.) Inui, N. (Cancer Inst., Japanese Fdn. Cancer Res. Toshima-ku, Tokyo, Japan) and S. Takayama. *Brit J Cancer* 25(3):574-583, 1971.

This report deals with the neoplastic transformation of hamster lung cells after exposure to cigarette condensate. Primary cultures of lung cells were obtained from suckling golden hamsters; tissue was minced into a slurry and subsequently explanted into supplemented McCoy's medium. Cells were cultured 7-15 days at 37°C in 5% CO<sub>2</sub>. For subculture, confluent cells were digested with trypsin and maintained in Mg<sup>++</sup>-and-Ca<sup>++</sup>-free Hank's solution. Cells were treated with cigarette tar dissolved in ethanol at a concentration of either 10  $\mu$ g/ml or 100  $\mu$ g/ml for 3  $\pm$  0.2 hr at 37°C in 5% CO<sub>2</sub>. Following exposure cells were washed, fresh culture medium added and cultures were continued at 37°C in 5% CO<sub>2</sub>. Untreated control cells were maintained *in vitro* for over 300 days. Tar-treated cells showed damage between two and 48 hours after treatment. Changes seen included nuclear pyknosis, cell necrosis, swelling and vacuolated cytoplasm. Transformation was noted after serial transfer *in vitro* for over 100 days. Here cells piled up on each other and formed dense colonies. None of these changes was noted in the control culture series. *In vivo* studies using transformed and control culture cells were carried



out. Cells were injected at one-month intervals into the cheek pouch of young hamsters from the 30th to the 191st day after treatment with tar. Animals inoculated with 100 µg/ml tar-treated cells developed tumors at the inoculation site. Histologic examination of tumor tissue indicated they were fibrosarcomas. Two possibilities are presented for the carcinogenic activity of the tobacco tar: 1) the tar contains nitroso compounds not yet identified; 2) the activity might be due to synergic action of carcinogenic hydrocarbons and nitroso compounds.

- 2333 EXPERIMENTAL ASBESTOS CARCINOGENESIS. (E.) Reeves, A. L. (Wayne St. U., Detroit, Michigan), H. E. Puro, R. G. Smith and A. J. Vorwald. *Environ Res* 4(6):496-511, 1971.

Experimental results on exposure of rats, rabbits, guinea pigs and hamsters to three types of asbestos dust, amosite, crocidolite and chrysotile, are presented. The minerals were ballmilled, forced through a 0.25-inch mesh screen, and disseminated into chambers containing the animals in the following concentrations (mg/m<sup>3</sup>): amosite, 48.2 ± 1.4; crocidolite, 48.7 ± 2.4; and chrysotile, 47.4 ± 1.7. Certain animals were also injected with the dusts to study the tissue reaction. Inhalation exposure to all three types of dust caused accumulation of hemosiderin-containing histiocytes, followed by fibrosis in the region of the terminal bronchiole in a few cases; squamous metaplasia was often prominent in this area, especially in the group exposed to crocidolite. Crocidolite and chrysotile both induced columnar-type metaplasia; no neoplasia was seen in the amosite group. Intratracheal injection of each of the dusts produced effects similar to those of inhalation. Intrapleural and i.p. injections effected histiocytic and foreign-body response, generally followed by fibrosis with occasional benign proliferative features. It cannot be definitely stated on the basis of experimental results that inhalation of crocidolite is more carcinogenic than amosite or chrysotile; however, it is concluded that amosite is less carcinogenic than crocidolite or chrysotile after being implanted into the pleura or peritoneum.

- 2334 POTENTIAL COCARCINOGENICITY OF SODIUM HYPOCHLORITE. (E.) Hayatsu, H. (Fac. Pharmaceut. Sci., Keio U., Tokyo, Japan), H. Hoshino and Y. Kawazoe. *Nature* 233(5320):495, 1971.

Results of tests using sodium hypochlorite as a cocarcinogen indicate that it is definitely involved in producing cancer in mice. Three groups of 40 5-wk-old ddN female mice were treated with a commercial sodium hypochlorite solution containing 10% effective chlorine, 4-nitroquinoline 1-oxide (4-NQO), or both chemicals. Tumors were induced only in those animals whose interscapular regions were painted with 4-NQO and then with hypochlorite solution; 9 of 32 animals so treated

developed skin tumors. No skin tumors were induced by painting with NaOH pH 11-12 and 4-NQO; thus the hypochlorite was the potential carcinogen and not the alkalinity of the solution. It is suggested that even though this common chemical is not a practical carcinogenic hazard, caution should be applied to its use.

- 2335 HEPATIC COPPER, MANGANESE, AND CHROMIUM CONTENT IN BRONCHOGENIC CARCINOMA. (E.) Morgan, J. M. (Vet. Admin. Hosp., Birmingham, Ala.). *Cancer* 29(3):710-713, 1972.

Hepatic concentrations of copper, manganese and chromium were measured in patients dying of carcinoma of the lung, with and without chronic bronchitis and emphysema, and in a group of controls. One hundred and four autopsies were available for hepatic tissue analysis. Four groups were studied: I) control group of 36 males; II) 26 males with proven emphysema and bronchitis; III) 19 males with proven emphysema and bronchogenic carcinoma; and IV) 23 males with no emphysema, but with proven lung carcinoma. No significant difference in copper concentration was seen among the different groups. Manganese content was found slightly increased ( $p = .05$ ) in Group III but was not significantly different in II or IV. Chromium concentration was significantly depressed in Groups III and IV ( $p = .01$ ) but the reason for this was not apparent.

- 2336 COUNTER-IMMUNOELECTROPHORESIS: RAPID METHOD FOR DETECTING GROUP-SPECIFIC ANTIGEN AND ANTIBODIES ASSOCIATED WITH ONCOGENIC RIBONUCLEIC ACID VIRUSES. (E.) Hoekstra, J. (Rush-Presbyterian-St. Luke's Med. Ctr., Chicago, Ill.) and F. Deinhardt. *Appl Microbiol* 22(6):1172-1173, 1971.

A simple, rapid and sensitive technique for the detection of group-specific (gs) antigens and antibodies, the counter-immunoelectrophoresis (CIEP) method, is described. When antisera to feline leukemia virus (FLV) were titrated against FLV gs antigen using complement fixation, gel diffusion, and CIEP, it was seen that titers found by CIEP were intermediate between those observed by the other two methods. Tissue homogenates clarified by homogenization revealed gs antigen by the CIEP method. Thus, CIEP may be used to detect gs antigens in various biologic samples.

- 2337 CHROMOSOMAL CONTROL OF CHEMICAL CARCINOGENESIS. (E.) Hitotsumachi, S. (Weizmann Inst. Sci., Rehovoth, Israel), Z. Rabinowitz and L. Sachs. *Int J Cancer* 9(2):305-315, 1972.

Studies are described which test a model for the genetic basis of malignancy. In that model, ex-

pression and suppression of transformed properties in cells depend on the balance between chromosomal factors, "S" and "E", responsible for suppression and expression, resp., of malignancy. Malignancy results from a change in chromosome balance, a change in which an excess of E over S is produced. Evidence for this model was sought using hamster cells transformed by dimethylnitrosamine (DMNA). Five variants of these cells were produced by seeding DMNA-transformed cells on X-irradiated rat embryo feeder layers. Variants were subcutaneously inoculated into hamsters and resulting cells from tumors, after being trypsinized and seeded, were 80% viable. While DMNA-transformed cells produced tumors in 100% of hamsters given s.c. inoculations of  $10^3$  transformed cells, cells of variant types showed reversion of properties of transformed cells, producing only 80-100% tumor incidence when inoculated in amounts of  $10^6$  cells/hamster. The chromosome constitutions of transformed and variant cells were examined and chromosomes were grouped (1-16) according to size and position of centromere. Changes in chromosome incidence among groups, particularly the increase in the number of group 5 chromosomes in transformed cells and the decrease in variants, indicate that chromosomes in group 5 may carry the factors for expression E. Restoration of tumorigenicity to cells of tumors produced by inoculation of variant cells was shown to be associated with chromosome loss in groups 7 and 9. This suggests that the S factor in the model is carried by chromosomes of groups 7 and 9. While DMNA-transformed cells were susceptible to treatment with 5-bromodeoxyuridine and visible light, variant cells were resistant to these treatments. However, variant-derived tumors showed the same susceptibility as transformed cells indicating that there are different E and S for different properties. It is hypothesized that carcinogens induced malignancy by causing chromosome rearrangements which affect S-E balance.

- 2338 SYSTEMATIC EFFECT OF TESTOSTERONE ON RAT LIVER TUMOR INDUCTION BY N-2-FLUORENYLACETAMIDE. (E.) Toh, Y.-C. (The Liverpool Clin., England) *J Nat Cancer Inst* 48(1):113-118, 1972.

Inbred Wistar male and female rats were castrated within 24 hr after birth and received either s.c. or intrasplenic implantation of testosterone pellets (20 mg in paraffin wax) on the 50th day of life. After one wk, they were given 8 mg N-2-fluorenylacetamide (FAA) by gastric intubation, twice a week for 25 wk; they were sacrificed at 48-50 wk of age. S.c. implantation of testosterone pellets greatly increased the incidence of all types of non-neoplastic (cysts, cirrhosis) and neoplastic (adenofibromas, pseudotubules, hyperplastic nodules and carcinomas) lesions of the liver in both male and female rats. No significant pathological changes were observed in control rats (given wax pellet only) or in rats receiving intrasplenic implantations of testosterone pellets. There were no significant differences in the final body weight between controls and testosterone-treated rats.

The weights of the thyroid and the pituitary glands in the rats receiving s.c. implantation were significantly less than those of the other groups. The levels of growth hormone in the rats receiving s.c. implantations, as assayed by the tibial width, were significantly higher than in any other group. The adenohypophyses of rats given testosterone implantations s.c. were compact in structure, with many acidophils and few or no castration cells. The glands of the controls and of the rats implanted with testosterone intrasplenically had a looser appearance with many castration cells and few glandular cells. Thyroid glands appeared similar in all groups. It is concluded that testosterone has no direct effect on FAA-induced liver carcinogenesis but acts indirectly via other endocrine glands, possibly the thyroid-pituitary system.

- 2339 ON THE CARCINOGENIC EFFECT OF 3,3'-DICHLORO-4,4'-DIAMINODIPHENYLMETHANE IN RATS. (Ger.) Steinhoff, D. (Inst. Exp. Path. Farbenfabriken Bayer AG, Wuppertal-Elberfeld, Germany) and E. Grundmann. *Naturwissenschaften* 58(11):578, 1971.

Two experiments carried out on male and female Wistar rats with different diets and doses of 3,3'-dichloro-4,4'-diaminodiphenylmethane (DMP) are described. Fifty rats maintained on low-protein diet were given a total dose of 27 g/kg body wt of DMP. Malignant tumors developed in 43 rats, with an average survival of 550 days. Multiple liver cell carcinomas with partial metastases were found in 40 cases. Primary lung tumor was observed in 13 rats with liver tumor in ten cases. Both liver and mammary carcinoma were found in one female rat. No tumors were observed in the control group. Another group of 34 rats was fed standard Altromin with natural ingredients and given s.c. injections of 500 and 1000 mg/kg body wt of DMP weekly or at longer intervals over 620 days, in a total amount of 25 g/kg body wt. With an average survival of 778 days, 29 malignant tumors were found in different organs of 22 animals. Liver cell carcinomas were determined in nine, and primary lung tumors in seven, cases. One malignant tumor was detected in the subcutaneous tissue. In the control group of 50 rats, 13 malignant tumors were detected after 1040 days, including one lung tumor and no liver tumors. Carcinomas developed earlier in the liver and lung with low-protein diets.

- 2340 MUTAGENIC PROPERTIES OF N-ACETYL-2-AMINOFLUORENE AND ITS METABOLITES IN RELATION TO THE MOLECULAR MECHANISMS OF CARCINOGENESIS. (E.) Fahmy, O. G. (Chester Beatty Res. Inst., London, England) and M. J. Fahmy. *Int J Cancer* 9(2):284-298, 1972.

The mutagenic effects of N-acetyl-2-aminofluorene (AAF) and synthetic derivatives of its suspected metabolites are examined. Mutagenic activity was examined in *Drosophila* with respect to point-mutations,



gene eliminations and chromosome breakage, in both the euchromatic and heterochromatic parts of the genome. Selective mutagenicity was assayed on the basis of the specific mutational effects on the *Minute (M)*, *bobbed (bb)* and three euchromatic loci relative to the overall X-chromosome response (recessive lethals and visibles) in the same sample of treated gametes. The parent carcinogen and its N-hydroxy derivatives (0.13 to 20 mM) were inactive as regards X-chromosome recessive mutations and heterochromatic deletions involving both the *M* loci and the fertility genes, but were decisively active with respect to the *bb*'s thus indicating their specificity for the r-RNA genes. The genetic activity of the 3-hydroxyamine was identical to that of the N-hydroxylamine (a possible conversion product), but the 1-hydroxy derivative was mutagenically ineffective. The highest mutagenic activity observed occurred with the amino-oxy esters. The acetic acid derivative -- N-acetoxy-2-acetylaminofluorene (N-AcO-AAF) -- exerted a wide spectrum of mutational effects: X-chromosome recessive mutations, heterochromatic gene eliminations (*M*'s and *bb*'s) and, to a lesser extent, chromosome structural rearrangements. Its ability to produce these classes depended on the germ cell stages, being maximal for point-mutations in the sperm and in the spermatids for the *M*'s and *bb*'s. The sulphate ester -- acetylaminofluorene-N-sulphate -- was considerably more selective for the heterochromatin than was N-AcO-AAF, as indicated by its high mutagenicity on the *M* loci and virtual inactivity with respect to the overall X-chromosome mutations. AAF and its N-hydroxylamines were also virtually specific for the *bb* loci, and N-AcO-AAF, which exerted its carcinogenicity at the site of injection, produced the same order of *bb*-selectivity as other direct carcinogens among the alkylating agents. These results are in agreement with the concept that mutations at the r-RNA genes might be significant in cancer initiation.

- 2341 ENZYMIC ACTIVATION OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE-1-OXIDE AND ITS INTERACTION WITH CELLULAR MACROMOLECULES. (E.) Tada, M. (Lab. Biochem. Aichi Cancer Ctr. Res. Inst., Nagoya, Japan) and M. Tada. *Biochem Biophys Res Commun* 46(2):1025-1032, 1972.

A cell-free system which activates 4-hydroxyaminoquinoline-1-oxide (4HAQO) to react with nucleic acid or protein is described. Rat ascites hepatoma cells (AH 130) were used as the enzyme and nucleic acid source. The amount of radioactivity of tritiated 4HAQO converted into an acid insoluble form was used to measure the binding of the carcinogen to nucleic acid. The binding activity was found in the 105,000 x g supernatant cytosol enzyme fraction of the AH 130 cell homogenate. Because ATP and Mg<sup>++</sup> were found to be definitely required for the reaction, it is suggested that a phosphotransferase catalyzes 4HAQO phosphate ester formation; this is then thought to react spontaneously with nucleic acid or protein. Paper chromatographic analysis showed that the cell-free system produced RNA and DNA adducts which were almost identical to those adducts formed *in vivo*.

- 2342 ACRYLAMIDE GEL ELECTROPHORESIS STUDIES OF THE INCORPORATION OF CYTIDINE-<sup>3</sup>H INTO MOUSE SKIN RNA AT EARLY TIMES AFTER TREATMENT WITH PHORBOL ESTERS. (E.) Baird, W. M. (U. Wisconsin Med. Ctr., Madison), P. W. Melera and R. K. Boutwell. *Cancer Res* 32(4):781-788, 1972.

Six- to eight-wk-old female Charles River CD1 mice pre-treated by a single injection of 7,12-dimethylbenz(a)anthracene received topical applications of four phorbol diesters or phorbol twice weekly. Controls were treated with acetone. Acetone, phorbol and phorbol-diacetate failed to induce papillomas by 24 wk. Sixty and 100% of mice treated with tetradecanoyl-phorbol-acetate and phorbol-didecanoate, resp., developed papillomas by 14 wk, whereas about 2% of those treated with phorbol-dibenzoate developed papillomas. The effect of a single topical application of 0.017  $\mu$ mole of each of these substances on incorporation of injected <sup>3</sup>H-cytidine into epidermal cell RNA was analyzed by polyacrylamide gel electrophoresis. All three tumor promoters produced a rapid, sustained increase in incorporation of label into total cell RNA. Tetradecanoyl-phorbol-acetate caused a three-fold increase in specific activity of 32S RNA, 18S and 28S rRNA and 4 to 5S RNA by 30 min after topical application, when compared to incorporation in acetone-treated controls. The increased incorporation into 32S RNA occurred before the increases in the other RNA species. By three hr, phorbol-didecanoate and phorbol-dibenzoate produced similar incorporation patterns, but of lesser magnitude. After a three-hr treatment, two irritants, acetic acid and cantharidin, produced slight increases in incorporation only into 4 to 5S RNA.

- 2343 DIFFERENT INCIDENCE OF BREAST CARCINOMAS OR FIBROADENOMAS IN DAUNOMYCIN OR ADRIAMYCIN TREATED RATS. (E.) Bertazzoli, C. (Farmitalia, Milan, Italy), T. Chieli and E. Solcia. *Experientia* 27(10):1209-1210, 1971.

An assessment of the carcinogenicity of the antibiotics daunomycin and adriamycin was carried out on female rats with a very low incidence of naturally occurring tumors. Seventy-five Sprague-Dawley rats were divided into three experimental groups: 1) 25 test animals received a single i.v. dose of 12.5 mg/kg of daunomycin; 2) 25 animals received a single i.v. dose of 8.0 mg/kg of adriamycin; and, 3) 25 animals were left untreated and maintained as controls. During a one-year period all animals were observed, and at the end of this time all survivors and controls were killed and examined. During the observation period 32 rats died. When examined, all showed severe renal damage and bone marrow aplasia. Observation showed that the first daunomycin-induced tumor appeared 94 days following injection and that the mean induction time for tumors was 121 days. The first adriamycin-induced tumor appeared 156 days after injection; the mean induction time was 223 days. This investigation showed the occurrence of a high rate of adenocarcinoma in daunomycin-treated animals and a high incidence of fibroadenomas in the adriamycin-treated group. None of the animals in the control series developed tumors.

- 2344 TUMOROUS DEVELOPMENT OF *IN SITU* AND GRAFTED ANTERIOR PITUITARIES IN FEMALE RATS TREATED WITH DIETHYLSTILBESTROL. (E.) Welsch, C. W. (Dept. Anat., Michigan St. U., East Lansing), T. Jenkins, Y. Amenomori and J. Meites. *Experientia* 27(11):1350-1352, 1971.

Seventeen female Sprague-Dawley rats were grafted with one pituitary underneath the kidney capsule; pituitary donor rats were of similar age, sex and strain as the recipients. Immediately after grafting, and for an additional three months, each rat was given an s.c. pellet of 12 mg diethylstilbestrol (DES). Sixteen months after the start of DES and the grafting, rats were killed and grafted and in situ pituitaries were observed for tumor development. Pituitaries greater than 50 mg in weight were designated as tumors. Transplanted pituitaries were receptive to DES tumorigenesis, but to a lesser degree than in situ pituitaries. Tumors developed in three of 17 grafts; each graft was markedly enlarged (mean weight =  $26.4 \pm 3.2$  mg). In situ pituitaries developed tumors in seven of 17 cases, and in situ pituitaries were more enlarged than grafted pituitaries (mean weight =  $63.5 \pm 11.2$  mg). No relationship between growth of in situ and grafted pituitaries was evident.

- 2345 CARCINOGENIC ACTION OF ESTROGENS. (E.) Herbst, A. L. (Boston, Mass.), H. Ulfelder and D. C. Poskanzer. *New England Med J* 285(20):1147, 1971.

In a letter to the editor, the authors refute a conclusion by Dunn (Letter to the Editor, *New Eng J Med* 285:1147) implicating estrogens in the etiology of certain cancers of the urogenital tract. The authors had previously reported (*New Eng J Med* 284:878 and 285:390, 1971) the occurrence of vaginal cancers in young women whose mothers had received stilbestrol during pregnancy. Dunn had obtained similar results in adult mice treated after birth with diethylstilbestrol or norethynodrel with mestranol. Using these two sets of results, Dunn concluded that if individuals of either species are exposed to an excess of estrogen, cancer may develop. The authors state that both stilbestrol and dienestrol (a chemically similar compound also implicated in the etiology of human vaginal cancers) are nonsteroidal compounds and that to date no data have been presented which implicate steroidal hormones with the etiology of human vaginal cancers. It is felt that the observed relation in humans between stilbestrol and vaginal cancer may be related to unique chemical properties of the stilbene molecule rather than to a nonspecific estrogenic effect.

- 2346 CARCINOGENIC ACTION OF ESTROGENS. (E.) Dunn, T. B. (Nat'l. Cancer Inst., Bethesda, Md.) *New Eng J Med* 285(20):1147, 1971.

In a letter to the editor, the effects of injecting diethylstilbestrol or norethynodrel with mestranol (Enovid) into newborn mice are described. Squamous-

cell carcinomas of the cervix and vagina and granular-cell myoblastoma at the cervix were found in female mice that survived to old age. Many of the male mice developed epididymal cysts. Stones of the vagina due to a congenital anomaly, and emptying of the urethra into the vagina were also seen. The histological appearance of the cervical and vaginal tumors seen in mice differed from that of adenocarcinomas of the vagina reported by Herbst, Ulfelder and Poskanzer (*New Eng J Med* 284:878 and 285:390, 1971) in young women whose mothers had received stilbestrol during pregnancy. The similarity of the effects on the vagina of estrogen injections into newborn mice and the vaginal changes described in human females whose mothers had received diethylstilbestrol indicate that if immature individuals of either species are exposed to an excess of estrogen, cancer may develop.

- 2347 THE EFFECT OF NEONATAL ADMINISTRATION OF SEX HORMONES ON RIBONUCLEIC ACID METABOLISM IN THE LIVER OF MALE AND FEMALE RATS. (E.) Toh, Y.-C. (The Liverpool Clinic, England) *Brit J Cancer* 25(3):516-519, 1971.

Male and female Wistar rats were injected s.c. within 24 hr after birth with either 500 µg testosterone propionate or 250 µg estradiol benzoate in arachis oil. Controls were untreated or received arachis oil alone. Half of each group were gonadectomized at four wk of age. When rats were 6-7 months old, each received an i.p. injection of  $\text{Na}_2\text{H}^{32}\text{PO}_4$  15 min before being sacrificed. The incorporation of  $^{32}\text{P}$  into nuclear RNA purified from liver homogenates was seven times greater in adult male controls than in adult female controls. Injection of estradiol into neonatal male rats reduced the subsequent uptake of  $^{32}\text{P}$  in adult life 2.5-fold when compared with controls. Neonatal administration of testosterone increased  $^{32}\text{P}$  incorporation in female rats 2.7-fold compared with controls but had no effect in males. Gonadectomy had no effect on the sex difference in  $^{32}\text{P}$  incorporation in control animals but did diminish the estrogen-induced decrease in  $^{32}\text{P}$  incorporation in male rats. Estradiol further decreased the uptake of  $^{32}\text{P}$  into nucleic acids of oophorectomized females. Testosterone administered neonatally produced a three- to sixfold increase in  $^{32}\text{P}$  incorporation in both male and female animals gonadectomized at puberty. These results indicate that the pattern of  $^{32}\text{P}$  incorporation into liver nucleic acids of adult rats is determined by the hormonal environment at about the time of birth.

- 2348 INVASIVE PROPERTIES OF HISTONE TRANSFORMED CELLS. (E.) Latner, A. L. (Royal Victoria Infirmary, Newcastle upon Tyne, England), E. Longstaff and J. M. Lunn. *Brit J Cancer* 25(3):568-573, 1971.

Four cell lines were examined for invasiveness in the presence and absence of rat liver histone. These were: (1) a line of neonatal kidney cells of unknown



karyotype, but originating from BHK21, which had been carried in monolayer culture for several years, designated BHK21 "X"; (2) a diploid line of BHK21; (3) a line of polyoma-transformed BHK21 cells (BHK21 Py); and (4) an epithelial-like polyploid cell line derived from human sternal marrow, designated Detroit 98. Sections of rat kidney cortex were then placed on the monolayers and after seven days the slices were removed and examined histologically for invasion by "normal" and "histone-transformed" cells. In the case of BHK21 "X", BHK21 and Detroit 98 cells, there was extensive invasion of histone-transformed cells into rat kidney cortex, whereas invasion by normal cells was minimal or nonexistent. Both non-transformed and histone-transformed BHK21 Py cells invaded the tissue slices to a considerable extent. No cellular invasion into totally necrotic tissues was noted and partially necrotic areas were bypassed by the invading cells. In the immediate area of the explant where individual Detroit 98 "sentinel" cells were invading, the tissue appeared necrotic.

- 2349 TUMORIGENESIS STUDIES WITH 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE, HYDRAZINE SULFATE, AND ISONICOTINIC ACID IN GOLDEN HAMSTERS. (E.) Toth, B. (U. Nebraska Coll. Med., Omaha). *Cancer Res* 32(4):804-807, 1972.

Solutions of 0.012% hydrazine sulfate (HS), 0.001% 1,2-dimethylhydrazine hydrochloride (1,2-DMH) or 0.5% isonicotinic acid (IA) were continuously added to the drinking water of five- to nine-wk-old, randomly bred, Syrian golden hamsters for the remainder of their lifetime. Consumption of HS and IA had no significant carcinogenic effect or effect on animal survival. 1,2-DMH, however, reduced survival and induced angiosarcomas of the blood vessels in 89% of the females and 82% of the males, with a mean latent period of 51 and 52 wk, resp. Thirty-four percent of females and 12% of males developed tumors of the cecum, with an average latent period of 61 wk. 1,2-DMH induced liver tumors in 20% of females and 14% of males.

- 2350 EXPERIMENTAL PANCREATIC TUMOR IN RATS AFTER INTRAVENOUS INJECTION OF 4-HYDROXYAMINOQUINOLINE 1-OXIDE. (E.) Hayashi, Y. (Shionogi Res. Lab., Osaka, Japan) and T. Hasegawa. *Gann* 62(4):329-330, 1971.

The relationship of intravenous injection of 4-hydroxyaminoquinoline 1-oxide to the incidence of pancreatic tumors in rats is studied. Sixty male and female Sprague-Dawley rats received 6-, 9- or 13-mg per kg body weight doses of the carcinogenic agent by injections into the tail vein. A control group of 20 male and 15 female rats were given intravenous injections of 0.5 ml of 0.005 N HCl. By seven days after treatment, 14 rats in the test group had died; at autopsy internal organs were seen to be edematous, the intestines were hemorrhagic and the lymphatic tissue was atrophied. A female rat which had received a 9 mg/kg dose was sacrificed at

162 days post treatment and leukemic infiltration of the vertebrae and peri-vertebral tissue was observed. Of the total initial test group, 35 animals survived beyond 165 days, with 26 animals developing tumors of the pancreas. Since pancreatic tumors are rare in rats, this experiment is considered significant because it establishes a technique by which the tumors can be induced.

- 2351 EFFECT OF LASIOCARPINE ON AFLATOXIN B<sub>1</sub> CARCINOGENICITY IN RAT LIVER. (E.) Reddy, J. K. (U. Kansas Med. Ctr., Kansas City) and D. Svoboda. *Arch Path* 93(1):55-60, 1972.

The combined effect of lasiocarpine (an inhibitor of liver cell division) and aflatoxin B<sub>1</sub> (a hepatocarcinogen) on rat liver was investigated. Sixty male Fisher-344 strain rats were divided into three groups of twenty animals each. Group I received aflatoxin B<sub>1</sub> at a dose of 2 ppm in their food. Group II received the same dose of dietary aflatoxin B<sub>1</sub> and biweekly i.p. injections of lasiocarpine in a dose of 7.8 mg/kg of body weight for 2 weeks and once a week for another 18 weeks. Group III received only the lasiocarpine injections at the same dosage bi-weekly for 4 weeks and once a week for an additional 52 weeks. Laparotomies were completed on the test animals at 4, 6, 10, 14, and 18 weeks. Aflatoxin alone (Group I) produced no liver change in the first six weeks of testing, nodules were visualized in a few instances at ten weeks and at 18 weeks well-developed nodules were seen in all animals. In Group II, liver cell necrosis was evident in six weeks, changes resembling postnecrotic cirrhosis were seen by ten weeks, and by 18 weeks hepatocellular carcinoma was noted in 16 of 19 rats. The animals in Group III had markedly enlarged liver cells by six to nine weeks, but by the 18th week neither cirrhosis nor nodularity was evident. These results indicate that lasiocarpine did not inhibit initiation of liver tumors by aflatoxin B<sub>1</sub>, but it did change the pathogenetic pattern in that the liver tumors were associated with marked postnecrotic cirrhosis.

- 2352 MALIGNANT TUMORS IN RATS GIVEN LASIOCARPINE. (E.) Svoboda, D. J. (U. Kansas Med. Ctr., Kansas City) and J. K. Reddy. *Cancer* 32(5):908-913, 1972.

A report of the possible carcinogenic effect of lasiocarpine is presented. Freshly prepared lasiocarpine was administered i.p. to 25 male Fischer rats in doses of 7.8 mg/kg body weight, twice weekly for four weeks and then once a week for an additional 52 weeks. A second group of 25 animals served as controls and was given 0.9% NaCl solution in doses of 0.1 ml/100 g body weight by i.p. injection. During the initial four week phase of the experiment 3 rats died of acute liver necrosis. At the end of the 56 week period 18 rats survived. Of these, 16 developed tumors between 60 and 76 weeks and 10 of these 16 had more than one tumor. In the surviving animals 61% (11 of 18) developed liver tumors,

33% (6 of 18) developed squamous cell carcinoma of the skin, and 28% (5 of 18) had pulmonary adenomas. The predominant histologic pattern was that of a well-differentiated trabecular hepatoma. The non-tumorous areas of the liver showed megalocytosis and conspicuous proliferation of the bile ducts. Squamous cell cancers appearing on the backs of the animals were all well differentiated with abundant keratin. Primary transplants from the liver tumors and squamous cell carcinomas were successfully transplanted and carried through five generations of animals. The findings in this study point clearly to the ability of lasiocarpine to induce malignant tumors in the liver and skin of rats.

- 2353 EVIDENCE FOR THE INACTIVATION AND REPAIR OF THE MAMMALIAN DNA TEMPLATE AFTER ALKYLATION BY MUSTARD GAS AND HALF MUSTARD GAS. (E.) Roberts, J. J. (Royal Cancer Hosp., London, England), T. P. Brent and A. R. Crathorn. *Europ J Cancer* 7(6):515-524, 1971.

The effects of mustard gas and half mustard gas on cell survival and DNA synthesis were determined in synchronous (obtained by selective detachment of mitotic cells) and asynchronous HeLa cell cultures. Although mustard gas was ten times more effective than half mustard gas, both produced the same effects. The effects of 0.075-0.625 µg/ml mustard gas on HeLa cell DNA synthesis were measured by the rate of <sup>3</sup>H-thymidine incorporation. There was an initial, rapid, dose-dependent inhibition which reached a maximum (40-85% of control) at about five hr and was followed by a period of constant or increased DNA synthesis for the next five hr. DNA synthesis began to decrease again over the next ten hr. When synchronous populations of HeLa cells were treated prior to DNA synthesis (early or late in G<sub>1</sub> phase), their progression into S phase was not delayed, but once they entered S phase, DNA synthesis was inhibited to different degrees, depending on the length of exposure. In cells treated in mid-S phase DNA synthesis was immediately inhibited by 70%. Cells in which the rate of DNA synthesis had been depressed exhibited a prolongation of the S phase and a corresponding mitotic delay. After the cells passed through a mitotic block, their subsequent progression through the cell cycle was the same as that of the controls. Although treatment of cells in G<sub>2</sub> phase did not delay the following mitosis, it did induce inhibition of DNA synthesis during the next cycle, which was then followed by a mitotic delay. Differences in viability and the rate of DNA synthesis indicated that cells treated early in G<sub>1</sub> phase were able to repair their DNA to a greater extent than cells treated later in G<sub>1</sub> phase. These results are consistent with the view that the cytotoxic action of mustard gas and half mustard gas is due to direct inactivation of the DNA template which can, however, be repaired.

- 2354 CHRONIC TOXICITY AND CARCINOGENICITY IN MICE OF THE PURIFIED MYCOTOXINS, LUTEO-

SKYRIN AND CYCLOCHLOROTINE. (E.) Uraguchi, K. (Dept. Path., U. Tokyo, Japan), M. Saito, Y. Noguchi, K. Takahashi, M. Enomoto and T. Tatsuno. *Ed Cosmet Toxicol* 10(3):193-207, 1972.

In long-term feeding studies initiated in 1960, a total of 287 ddNi and 57 ddN mice were fed grain diets containing either luteoskyrin (LS, 0-500 µg/day) or cyclochlorotine (CC, 0-60 µg/day). LS and CC were obtained from a strain of *Penicillium islandicum*, a fungus which infects so-called "yellowed rice". Toxic responses to LS and CC, and liver tumorigenesis, were observed. Liver changes produced by LS and CC included: acute and subacute liver necrosis, subchronic liver necrosis, chronic liver injury (i.e., advanced pleomorphism of liver cell nuclei), and hepatoma. Acute, subacute and subchronic liver necrosis were seen in ddNi mice given 50-500 µg LS/day and dying before 190 days. Lesions were more prominent in mice given larger amounts of LS. Necrosis was more prevalent in male than in female ddNi mice given 150 µg LS/day. The incidence of chronic liver injury was similar in both sexes. Hepatomas were induced by both LS and CC in a dose-response manner in mice surviving for 216 days. Hepatomas developed more frequently in males than in females given 150 µg LS/day. The acute effects of the two mycotoxins differed in that necrosis was seen in early stages in mice given LS, while fibrosis and cirrhosis were more common in mice given CC. Chronic effects of LS and CC were similar. LS and CC were thought to be responsible for the known hepatotoxic and hepatocarcinogenic effects of yellowed rice.

- 2355 HISTOPATHOLOGIC STRUCTURE OF ADENOCARCINOMAS INDUCED IN GLANDULAR STOMACH OF RAT BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Sato, T. (Tohoku U. Sch. Med., Sendai, Japan). *Tohoku J Exp Med* 105(3):201-221, 1971.

A total of 126 female Donryu rats were given N-methyl-N'-nitro-N-nitrosoguanidine in drinking water (0.017% or 0.010%), and tumor development in the stomachs of 85 rats was observed. Seventy-two rats had a total of 129 gross stomach lesions. There was no significant difference in the incidence of gastric lesions in rats given different doses of carcinogen. Most lesions (89.1%) were in the pyloric antrum. Lesions ranged from those without cellular atypism, through those with slight or marked atypism, to those which were considered malignant. Adenocarcinoma was usually recognized in the stomachs of rats fed the carcinogen for ten or more months. Forty-eight adenomatous hyperplasias and 21 adenocarcinomas were seen. Adenocarcinomas at various stages of development in rat stomachs were thought to preserve the growth pattern of the adenomatous hyperplasias from which they developed. Three patterns of growth of adenocarcinomas were distinguished. In "Series A", stomach lesions proliferated horizontally, penetrated muscularis mucosae, and invaded submucosa in a caisson-like fashion. In "Series B", lesions grew upward in a polypoid fashion. In "Series C", lesions grew downward in an "iceberg-like" fashion, penetra-



ting muscularis mucosae, and developing into carcinoma at the bottom of the "iceberg". The three growth patterns resulted in lesions resembling Bormann human gastric carcinomas of types III, I and II, resp.

- 2356 EFFECT OF PLURONIC-F68 ON THE DEVELOPMENT OF TUMOR METASTASIS. (E.) Silk, M. (VA Hosp., Newington, Conn.) and E. Sigman. *Cancer* 29 (1):171-172, 1972.

Pluronic-F68 (PLF-68) is a nonionic surface agent that decreases blood viscosity and platelet adhesiveness. Previous studies have shown that treatment with agents which either interfere with the clotting mechanism or reduce blood viscosity can decrease the incidence of tumor metastasis. The effect of PLF-68 on the development of tumor metastasis was therefore investigated. Sixty-five adult male rats were injected in the tail vein with 1 ml of Walker 256 ascitic tumor (100,000 cells/ml). Thirty-one of these animals received 4 mg/100g body wt of PLF-68 i.v. each day for seven days prior to and for seven days following tumor inoculation. All animals that died were necropsied and rats surviving at the end of the eight wk were sacrificed. The incidence of metastases in the controls was 85.3% as compared to 16.1% in PLF68-treated rats ( $P > 0.01$ ). Further, 80% of PLF68-treated rats survived eight wk compared to 23% of the control group ( $P > 0.01$ ). Since PLF68 does not cause bleeding and appears to have no clinical side effects, it is suggested that PLF68 may eventually prove useful at time of surgery to prevent metastasis secondary to operative tumor manipulation.

- 2357 SIALIC ACID IN HUMAN CANCER. (E.) Mabry, E. W. (U. Oklahoma Sch. Med., Oklahoma City) and R. Carubelli. *Experientia* 28(2):182-183, 1972.

The two main sialic acids, N-acetyl-neuraminic acid (NANA) and N-glycolyl-neuraminic acid (NGNA), were assayed in purified homogenates of cancer tissues and of normal tissues obtained from autopsies of cancer and non-cancer patients. The sialic acid content was liberated by heating, purified on Dowex columns, and identified by paper chromatography, using the thiobarbituric acid method. Analysis of malignancies of pancreas (adenocarcinoma), liver (metastasis from pancreatic adenocarcinoma), skin (squamous cell carcinoma) and lymph node (metastasis from skin melanoma) showed that NANA levels were elevated two-to fourfold as compared with normal tissues. No NGNA was detected in any of the normal or cancerous tissues. Although NGNA has been found by other investigators in rat hepatomas and in the HeLa S-3 cells (a cell line of human cancer origin), these results indicate that both normal and cancerous human tissues contain only NANA.

- 2358 GROWTH CHARACTERISTICS OF THE STILBESTROL-INDUCED HAMSTER KIDNEY TUMOR. (E.)

DeKernion, J. B. (Natl. Cancer Inst., Bethesda, Md.) and E. E. Fraley. *J Surg Oncology* 3(5):507-515, 1971.

This investigation was undertaken to determine the effect of diethylstilbestrol (DES) on the growth of an estrogen induced kidney tumor *in vitro* and *in vivo*. Primary tumors were induced in hamsters by s.c. transplant of two 12 mg DES pellets. Ninety per cent of the animals had detectable tumors in 280 days. Tumor propagation was carried out by s.c. trocar implant of 2-3 mm tumor slices from the primary tumor into the left lumbar region of test animals. In the transplant group, 10th to 14th generation tumors grew rapidly with 1-2 cm masses forming in 14 to 20 days. Hormone dependence persisted and tumors uniformly atrophied when DES was withdrawn. Viable tumor tissue was excised from the centers of either primary or transplant tumors and suspended in a medium with antibiotics, then incubated at 37°C. The medium was changed daily until a confluent monolayer formed, then cells were suspended with 9.25% trypsin and subcultured in RPMI 1640 with antibiotics and 20% calf serum. DES dissolved in 70% ethyl alcohol was added to culture medium in concentration of 2,4,5,6 and 8 g DES/ml., and viable kidney culture cells were introduced into the flask. Two controls were prepared, one with media containing neither DES nor alcohol, the other with 0.13 and 0.5% ethanol but no DES. Each experimental group (two controls and one test unit) was prepared in quintuplet and all were simultaneously incubated at 37°C. Initially, explants grew well *in vitro*, with confluent monolayer formation occurring in 4-6 days. Attempts to propagate cell lines longer than five subcultures failed; most cells died after the second subculture. DES in the concentrations used had no influence on growth rate and the survival time did not increase. Sufficient cells to conduct further experiments could not be harvested. Response to DES appears to be peculiar to the hamster. This study revealed that continued growth is hormone-dependent *in vivo*. As yet unidentified stromal or humoral factors are probably important constituents of the complex series of events leading to renal cell transformation by sex hormones.

- 2359 STUDIES OF THE GOITROGENIC AND ONCOGENIC EFFECT OF METHYLTHIOURACIL IN C<sub>3</sub>H MICE. (E.) Jemec, B. (Fibiger Lab., Kgs. Lyngby, Denmark). *Acta Path Microbiol Scand* 79:545-552, 1971.

A study was performed to determine (1) the goitrogenic and oncogenic effect of methylthiouracil (MTU) on C<sub>3</sub>H mice and (2) the effect of MTU and Thycapzol (1-methyl-2-mercapto-imidazol) on thyroid hormone production. MTU or Thycapzol were administered in drinking water to two groups of C<sub>3</sub>H/FIB mice with a third group receiving neither drug serving as a control. No carcinogenic effect was detected in any of the groups. However, thyroid hormone production was depressed by both MTU and Thycapzol as indicated by the T<sub>3</sub> serum test. The data obtained suggest no direct correla-

tion between the antihormonal and goitrogenic effect of the two compounds.

- 2360 EFFECT OF FEEDING N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]FORMAMIDE ON MITOTIC ACTIVITY OF RAT URINARY-BLADDER EPITHELIUM. (E.) Tiltman, A. J. (St. Vincent Hosp., Worcester, Mass.) and G. H. Friedell. *J Nat Cancer Inst* 48(1):125-129, 1972.

Normal circadian variation in the mitotic activity of rat bladder epithelium was determined in male Fischer rats by a colchicine metaphase-arrest technique, and it was found that this activity reached a maximum ( $0.399 \pm 0.160/1000$  cells/hr) between 5:00 and 9:00 a.m. and dropped thereafter. Mitotic indices of bladder epithelium were also determined four and 25 wk after rats were placed on a diet containing 0.188% N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide. Although mitotic indices of the carcinogen-fed rats determined at 9:00 a.m. and 7:00 p.m. were significantly higher than those of the controls, no circadian variation was present. All the carcinogen-fed rats autopsied at 25 wk had at least one bladder tumor (transitional, squamous or mixed), whereas the controls had none. The mitotic indices of the different tumor types showed similar values which were markedly higher than the adjacent nontumorous bladder epithelium.

- 2361 TRITON WR 1339 (TWR), AN INHIBITOR OF CANCER DISSEMINATION AND METASTASES. (E.) Franchi, G. (Istituto de Ricerche Farmacologiche, Milan, Italy), L. Morasca, I. R-D-Innocenti and S. Garattini. *Europ J Cancer* 7(6):533-544, 1971.

Tests are reported which indicate that Triton WR 1339 (TWR), a formaldehyde polymer of polyoxyethylene ether of octylphenol, decreases cancer dissemination and metastases. A wide series of experiments carried out *in vivo* included: 1) C57/B1/10J/Sel mice injected in the leg muscle with Lewis lung cancer; 2) Swiss albino mice injected intratibially with Ehrlich carcinoma; and 3) Swiss albino mice injected intracerebrally (i.c.) with Sarcoma 180. Control mice were maintained at all phases of this testing. All test mice were injected with either 500, 200 or 50 mg/kg doses of TWR i.p. Examination of their tissues indicated a decrease in the formation of metastases. This antimetastatic activity was not accompanied by a reduction of the initially induced primary node. Test animals with tumors induced in s.c. and i.p. sites by injection of Ehrlich carcinoma or Sarcoma 180 indicated TWR to be ineffective in preventing metastases. *In vitro* experiments were conducted, using separate cultures of normal human embryonal epithelium, human carcinoma of the pharynx, rhabdomyosarcoma of WAG/Rij (BA 1112) rats, and Ch. L. Ching liver cells derived from normal human liver lines. Concentrations of  $2 \times 10^5$  cells/ml to which 1 mg/ml dose of TWR was added were maintained at 37°C temperature in 5% CO<sub>2</sub>. Results on this series of tests indicated affected

adhesiveness of the carcinoma cells by an alteration of the cell membrane, thus cell volume was increased sufficiently to markedly reduce cancer cell movement. Review of all test data indicated that the antimetastatic activity observed in TWR involves enhancement of reticuloendothelial system activity, initiating host reaction to tumor in a "foreign particle" manner, and by decreasing cell movement through membrane-volume action which makes cells highly susceptible to host reaction.

- 2362 MORPHOLOGICAL DIFFERENTIATION INDUCED BY PROSTAGLANDIN IN MOUSE NEUROBLASTOMA CELLS IN CULTURE. (E.) Prasad, K. N. (U. Colorado Med. Ctr., Denver). *Nature New Biol* 236(63):49-52, 1972.

Addition of prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) to cultures of uncloned neuroblastoma cells 24 hr after seeding induced morphological differentiation, as evidenced by axon formation. The differentiated cells showed morphological maturation, as shown by an increase in the nuclear and cellular size. The presence of PGE<sub>1</sub> during the entire period of observation was necessary for maximum effect (10 µg/ml for 3-5 days). PGE<sub>1</sub> also produced morphological differentiation in two neuroblastoma clones (NBA<sub>5</sub> and NBA<sub>2</sub>). PGE<sub>2</sub> was just as effective in inducing differentiation as was PGE<sub>1</sub>, whereas PGE<sub>2α</sub> at a similar concentration was ineffective. Cells grown in PGE<sub>1</sub> grew at about the same rate as controls for one day and reached a plateau two days later. Removal of the drug and readdition of fresh medium three days later slightly increased the growth rate as compared with cells from which PGE<sub>1</sub> was not removed. By 10 days after removal of PGE<sub>1</sub>, most of the differentiated cells had died, indicating that PGE<sub>1</sub>-induced differentiation was irreversible. Addition of vinblastine sulfate, which is known to interfere with the assembly of microtubules, along with PGE<sub>1</sub> prevented axon formation, indicating that PGE<sub>1</sub> promoted the organization of microtubules necessary for differentiation. Incubation of PGE<sub>1</sub>-treated cells with either actinomycin D or cycloheximide showed that PGE<sub>1</sub>-induced axon formation required synthesis of new protein but not of new RNA. These results indicated that induction, as well as expression of morphologically differentiated phenotype, might be controlled at the translation rather than at the transcription level and that inhibition of cell division of neuroblastomas might be secondary to the induction of axon formation.

- 2363 SOME EFFECTS OF 2,4-D AND 2,4,5-T ON EHRlich ASCITES TUMOR CELLS *IN VIVO* AND *IN VITRO*. (E.) Walker, E. M. (Med. U. So. Carolina, Charleston), R. H. Gadsden, L. M. Atkins and G. R. Gale. *Industrial Med* 41(1):22-27, 1972.

Daily i.p. injection of the herbicides, 2,4-D or 2,4,5-T, into Ehrlich ascites tumor-bearing mice inhibited further tumor growth from 30 to 73% compared with untreated controls. The 2,4,5-T was slightly more effective than 2,4-D. Both compounds prolonged survival time of tumor-bearing



- rats, with 2,4,5-T again being slightly more effective. Injection of 2,4-D 48 hr prior to injection of sodium formate- $^{14}\text{C}$  stimulated labeling of RNA guanine by 16% and RNA adenine by 8%. However, injection of 2,4,5-T 48 hr prior to labeled formate produced an average 28% inhibition of RNA adenine synthesis and 30% inhibition of RNA guanine synthesis, suggesting inhibition of *de novo* purine synthesis at some step prior to inosinic acid. The effects of 2,4-D and 2,4,5-T were studied on *in vitro* incorporation of  $^3\text{H}$ -thymidine,  $^3\text{H}$ -uridine and  $^{14}\text{C}$ -leucine into ascites cell DNA, RNA and protein, resp. Incubation for one hr or less with 2,4-D did not significantly increase DNA, RNA or protein synthesis; however, incubation for two hr increased them by 17, 37 and 22%, resp. Incubation with 2,4,5-T for one hr produced slight increases of incorporation of label into DNA and RNA; incubation for two hr did not further increase DNA synthesis and decreased RNA synthesis to below control values. 2,4,5-T stimulated protein synthesis by 23 and 28% after one and two hr, resp. It is concluded that the extent of the effects on DNA, RNA and protein synthesis are not adequate to explain the relatively marked and significant degrees of inhibition of tumor development *in vivo*.
- 2364 THE STRUCTURE OF THE THYMINE:3,4-BENZOPYRENE PHOTOPRODUCT. (E.) Blackburn, G. M. (Dept. Chem., U. Sheffield, England), R. G. Fenwick and M. H. Thompson. *Tetrahedron Lett* 7:589-592, 1972.
- 2365 INTRACRANIAL TUMORS IN MICE OF TWO DIFFERENT STRAINS MAINTAINED ON FAT ENRICHED DIETS. (E.) Szepeswol, J. (U. P. R. Sch. Med., San Juan, Puerto Rico). *Europ J Cancer* 7(6):529-532, 1971.
- 2366 FURTHER STUDY ON THE PROPERTIES OF THE RAT LIVER PROTEIN INVOLVED IN A PARAMAGNETIC COMPLEX IN THE LIVERS OF CARCINOGEN-TREATED RATS. (E.) Chiang, R. W. (Dept. Biol., Washington, U., St. Louis, Mo.), J. C. Woolum and B. Commoner. *Biochim Biophys Acta* 257(2):452-460, 1972.
- 2367 ONCOGENICITY OF IMMUNOSUPPRESSIVE DRUGS. (E.) McEwan, A. (Wellcome Res. Lab., Beckenham, Kent.) and L. G. Petty. *Lancet* 1(7745):326-327, 1972.
- 2368 COMPARISON OF THE EFFECTS OF CYSTEINE UPON THE DECOMPOSITION OF NITROSOUREAS AND OF 1-METHYL-3-NITRO-1-NITROSOGUANIDINE. (E.) Wheeler, G. P. (Southern Res. Inst., Birmingham, Ala.) and B. J. Bowdon. *Biochem Pharm* 21(2):265-267, 1972.
- 2369 3-METHYLCHOLANTHRENE BLOCKS HEPATIC NECROSIS INDUCED BY ADMINISTRATION OF BROMOBENZENE OR CARBON TETRACHLORIDE. (E.) Reid, W. D. (Natl. Heart Lung Inst., Bethesda, Md.), B. Christie, M. Eichelbaum and G. Krishna. *Exp Molec Path* 15(3):363-372, 1971.
- 2370 EXCRETION AND CONVERSION OF 3-METHYLCHOLANTHRENE METABOLITES IN THE INTESTINAL TRACT OF THE MOUSE. (E.) Takahashi, G. (Chest Dis. Res. Inst., Kyoto U., Japan) and K. Yasuhira. *Cancer Res* 32(4):710-715, 1972.
- 2371 CHARACTERIZATION OF PROTEIN AND DNA IN P815 CELLS SENSITIVE AND RESISTANT TO 1- $\beta$ -D-ARABINOFURANOSYLCYTOSINE. (E.) Kreis, W. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.), D. Drahovsky and H. Borberg. *Cancer Res* 32(4):696-701, 1972.
- 2372 N-DIMETHYLNITROSAMINE IN TOBACCO SMOKE CONDENSATE. (E.) Rhoades, J. W. (Southwest Res. Inst., San Antonio, Texas) and D. E. Johnson. *Nature* 236(5345):307-308, 1972.
- 2373 CARCINOGENIC NITROGEN COMPOUNDS: PART LXXV. SKRAUP REACTIONS WITH SOME POLYCYCLIC AMINES, AND TWO CASES OF ANTI-MARCKWALD ORIENTATION. (E.) Buu-Hoi, N. P. (Inst. Chem. Nat. Substances, Gif-sur-Yvette, France), P. Jacquignon, D. C. Thang and T. Bartnik. *J Chem Soc Pekin Trans I* 1(2):263-265, 1972.
- 2374 EARLY REACTIONS OF THE SUBCUTANEOUS TISSUE TO REPEATED INJECTIONS OF CARCINOGENS IN AQUEOUS SOLUTIONS. (E.) Hooson, J. (British Industrial Biol. Res. Ass., Carshalton, England), P. Grasso and S. D. Gangolli. *Brit J Cancer* 25(3):505-515, 1971.
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See also:

- \* (Rev): 2215, 2222, 2230, 2234, 2247, 2250, 2251, 2257, 2265, 2277, 2278, 2285
- \* (Viral): 2486, 2493, 2500, 2512
- \* (Immun): 2615, 2636, 2667
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A case of premalignant fibroepithelioma, an uncommon (49 cases reported in the past 19 yr) variant of basal cell carcinoma, is reported in a 40-year-old Spanish-American male. A 15 x 10 x 3 mm tan, firm, polypoid cutaneous nodule, with a finely lobulated surface, was removed from the right groin 14 yr after radical orchiectomy and radiation therapy (2800 r) for seminoma. Microscopically, the nodule consisted of anastomosing, long, thin columns of basaloid cells with foci of peripheral palisading in an abundant cellular fibrous stroma. Some of the basocellular columns arose from the overlying narrow epidermis. The adjacent epidermis was moderately melanin-pigmented and had well-preserved rete pegs and skin appendages. No additional skin lesions have developed since excision of the first lesion. Review of the 49 other cases of premalignant fibroepithelioma has revealed a predilection for the lumbosacral region and the 50-79 yr age group, but was no sex predilection. About 40% had multiple lesions and all tumors were less than four cm. Four patients had a previously excised visceral carcinoma, three of which were of the genitourinary tract.

- 2453 THE FORMATION OF SINGLE-STRAND BREAKS IN INTRACELLULAR DNA BY X-RAYS. (E.) Johansen, I. (Div. Toxicol., Norwegian Defense Res. Est., Kjeller), I. Gurvin and W. D. Rupp. *Radiat Res* 48(3):599-612, 1971.

Three different strains of  $\lambda$  bacteriophages were isolated from *E. coli*, labeled, and subjected to x-irradiation to rupture the phosphodiester chains in the DNA. It was found by density gradient centrifugation that the phage  $\lambda$  DNA sedimented into two components: 1) a slowly sedimenting component which included single-stranded circular and linear DNA, and 2) a rapidly sedimenting component which contained the double-stranded, covalently-bonded, circular DNA. Further experiments indicated that rejoining of the strand breaks induced by the x-irradiation was very rapid under rich growth conditions; about two-thirds of the broken structures were converted in the first 100 seconds. A significant, but much slower, rate of repair occurred when the cells were kept in phosphate buffer solution at freezing temperature. Rejoining of strand breaks also occurred when starvation and heat shock were used prior to the irradiation. The  $\lambda$  DNA structures were 3.3 times more sensitive to single-stranded breakages under full oxygenation than under nitrogen.

- 2454 NEUTRON-INDUCED MAMMARY NEOPLASMS IN THE RAT. (E.) Vogel, H. H. Jr. (U. Tennessee Coll. Med., Memphis). *Cancer Res* 32(5):933-938, May 1972.

This report discusses an experiment comparing the

effect of fission neutrons with low linear energy transfer radiation in the production of mammary neoplasia in rats. Female Sprague-Dawley/ANL rats, two to three months old, were exposed to single whole body doses of fission neutrons at a rate of 7 to 11 rads/min. Unirradiated rats were maintained as controls. All animals were retained for the length of their lives. Results following exposure showed that 85% of the neutron-exposed rats developed palpable tumors. This percentage among the neutron-irradiated animals is higher than in a similar group which was exposed to 100 R of X-rays over their entire lifespans. The unirradiated controls showed that only two of a total of 89 rats developed mammary neoplasm within one year. It was concluded that induction of mammary neoplasms in the rat shows extreme sensitivity to irradiation with low doses of fast neutrons, and that in light of current interest in the use of neutrons in human radiation therapy, a conservative approach is mandatory until more data on the radiobiology of fission neutrons is acquired.

- 2455 CARCINOMA OF THE LIVER. (E.) Jordan, S. W. (U. New Mexico Sch. Med., Albuquerque). *Human Path* 2(4):533-534, 1971.

This study delineates epidemiologic factors in primary cancer of the liver on the basis of 2457 autopsy series completed in Hiroshima and Nagasaki. Included in the series are persons exposed to atomic bomb radiation in 1945 under known conditions as well as individuals who were not exposed. The incidence of cirrhosis of the liver is found to be the same in both cities. Carcinoma of the liver is more common in Nagasaki than in Hiroshima for both males and females 50 years of age or older. No significant difference is found between carcinoma of the liver or cirrhosis and socioeconomic parameters such as occupation, family income, amount of living space, diet, alcohol consumption or smoking. Therefore, the increased rate of primary liver cancer in Nagasaki is felt to be partly explicable on the basis that cirrhosis is more likely to be associated with hepatoma in Nagasaki than in Hiroshima. It is also noted that among noncirrhotic subjects, hepatoma is twice as prevalent in Nagasaki.

- 2456 SYNERGISTIC EFFECT OF AN *ESCHERISCHIA COLI* MUTATOR GENE ON MUTAGENESIS BY ULTRAVIOLET RADIATION AND BY ALKYLATING AGENTS. (E.) Hill, R. F. (Dept. Biol., York U., Toronto, Ontario, Canada). *Mutat Res* 14(1):23-31, 1972.

The interactions of a bacterial mutator gene, the *mut H<sub>1</sub>* gene located in the *lys-cys* region of the *E. coli* chromosome, were studied. Induction of prototrophic suppressor mutations was also studied. UV radiation and the alkylating agents, ethyl methanesulfonate and methyl methanesulfonate, were used for the mutability studies. The probability of a synergistic effect for UV-induced Gal<sup>-</sup> mutations was



found to be 0.984. Using *uvr mut<sup>+</sup>* compared with *uvr mut* strains the ratio of yields increased from 2.3 to 3.8. Further experiments using all three exogenous mutagenic agents produced a larger number of mutants with impaired carbohydrate-fermenting ability when the mutator allele rather than the wild-type allele was present. The *mut H1* gene product may therefore increase the probability of replication errors due to changes in the structures of the DNA template. No synergistic effect for UV-induced suppressor mutations was demonstrated; this may have been due to the method used for scoring mutants.

- 2457 ANASTOMOTIC SARCOMA OF IRRADIATED PARABIONT RATS. (E.) Warren, S. (New Eng. Deaconess Hosp., Boston, Mass). *Cancer Res* 32(5):983-987, 1972.

Incidence of the development and localization of mesenchymal sarcomas in anastomotic sites is observed. The right partner in surgically parabiont rats was exposed to 1000 rads of total-body radiation. Among 1003 parabiontly paired test animals, an excessive number of rapid growth sarcomas appeared in the connective tissue and muscle as opposed to sarcomas in 128 unirradiated pairs. Results showed 87 anastomotic sarcomas developing at the surgical site. Histological studies classified them as 64 fibrosarcomas, ten undifferentiated sarcomas, eight rhabdomyosarcomas, three extraosseous osteogenic sarcomas, one angiosarcoma and one myxosarcoma. In addition, the irradiated partners developed primary benign and malignant tumors at various sites, many occurring in the endocrine organs. Factors accounting for the increased number of sarcomas were judged to be irradiation, hormonal environment, and regional density of scar tissue at the anastomotic site. Coincidental to radiation and surgical factors, an increase in the levels of circulating gonadotropins was observed and is considered to be the result of altered feedback from gonads, adrenals, and pancreas.

- 2458 INDUCTION OF GIANT CELLS IN SUSPENSION CULTURES OF *ARACHIS HYPOGAEA*, L. BY MASSIVE IRRADIATION. (E.) Verma, D. P. S. (Dept. Plant Sci., U. Western Ontario, London, Canada) and R. B. van Huystee. *Radiat Res* 48(3):518-530, 1971.

A study of the effects of massive irradiation on suspension cultures of V-56R peanut cells *Arachis hypogaea*, L. is reported. Protein synthesis was affected only by radiation doses greater than 50 krad. Protein synthesis continued at 45-55% of controls at a dose of 500 krad if the cells were incubated in fresh medium after irradiation and showed an apparent recovery during postirradiation period. Massive doses of irradiation (50-500 krad) arrested cell division but not synthesis of cellular constituents; the cells became elongated and proteins accumulated. There was an apparent recovery in protein synthesis during the postirradiation period, but the cells had lost their reproductive potential, resulting

in giant cell formation and later cell death. The effect of radiation on protein synthesis was also dependent on the age of the cultures and the presence of conditioned medium during irradiation. The uptake of leucine was not affected by radiation if the cells were incubated in fresh medium after irradiation. Growth, protein synthesis and recovery were also affected by irradiation of the medium.

- 2459 EFFECT OF RADIATION ON LYMPHOCYTES: ABOLITION OF THE PHENOMENON OF ALLOGENEIC STEM CELL INACTIVATION. (E.) Manyko, V. M. (Inst. Biophys., Ministry Public Hlth. USSR, Moscow). *Folia Biol* 17(6):365-369, 1971.

- 2460 BREAST CARCINOMA 30 YEARS AFTER THOROTRAST MAMMOGRAPHY. (E.) Ailmed, M. Y. (Kingston Gen. Hosp., Ontario, Canada) and H. D. Steele. *Can J Surg* 45-49, 1972.

- 2461 RADIATION-INITIATED DNA SYNTHESIS IN SPERMATOGENIC CELLS OF THE MOUSE. (E.) Kofman-Alfaro, S. (Western Gen. Hosp., Edinburgh, Scotland) and A. C. Chandley. *Exp Cell Res* 69(1):33-44, 1971.

- 2462 THE EFFECT OF  $\gamma$  RADIATION ON THE STRUCTURE OF DNA AND THE DEOXYRIBONUCLEOPROTEIN ISOLATED FROM IRRADIATED LYMPHATIC GLANDS. (E.) Tyrawska-Spychalowa, D. (Dept. Biophys., U. Lodz, Poland), B. Grabowska, B. Rozga and A. Kaminska. *Biochim Biophys Acta* 254(1):40-47, 1971.

- 2463 IONIZING RADIATIONS AND THE CELL CYCLE. (E.) Tolmach, L. J. (Sch. Med., U., St. Louis, Mo.), B. G. Weiss and L. E. Hopwood. *Fed Proc* 30(6):1742-1751, 1971.

- 2464 ALPHA-RAY INDUCED BREAKS IN THE DNA OF *Escherichia coli*. (E.) Wilkins, R. J. (Wakari Hosp., Dunedin, New Zealand). *Int J Radiat Biol* 20(5):497-500, 1971.

- 2465 ON THE MECHANISM OF THE RADIATION-INDUCED INACTIVATION OF RIBONUCLEASE IN DILUTE AQUEOUS SOLUTION. (E.) Adams, G. E. (Mount Vernon Hosp., Northwood, Middlesex, England), R. L. Willson, R. H. Bisby and R. B. Cundall. *Int J Radiat Biol* 20(5):405-415, 1971.

- 2466 RADIOACTIVE CONTAMINATION OF THE SKIN. (E.) Schofield, G. B. (U. K. Atomic Energy Author., Sellafield, England). *J Soc Cosmet Chem* 22(8):535-545, 1971.

- 2467 RADIATION-INDUCED DNA SYNTHESIS IN NORMAL AND STIMULATED HUMAN LYMPHOCYTES. (E.) Darzynkiewicz, Z. (Boston Biomed. Res. Inst., Mass.). *Exp Cell Res* 69:356-360, 1971.

- 2468 RADIATION INDUCED MENINGEAL FIBROSARCOMA. (E.) Schrantz, J. L. (U. Arkansas Med. Ctr., Little Rock) and C. A. Araoz. *Arch Path* 93(1):26-31, 1972.
- 2469 CASE REPORTS: RADIATION CANCER OF THE THORACIC OESOPHAGUS. (E.) Chudecki, B. (Royal Devon Exeter Hosp., England). *Brit J Radiology* 45(532):303-304, 1972.
- 2470 OSTEOGENIC SARCOMA OF THE SKULL: A RARE SEQUELA OF PITUITARY IRRADIATION. (E.) Sparagana, M. (Chicago Med. Sch., Ill.), R. W. Eells, S. Stefani and V. Jablokow. *Cancer* 29(5):1376-1379, 1972.
- 2471 CHILDHOOD CANCER FOLLOWING OBSTETRIC RADIOGRAPHY. (E.) Stewart, A. M. (Dept Social Med., Oxford U., England), G. J. Draper and G. W. Kneale. *Lancet* 2(7739):1424, 1971.
- 2472 A CASE OF CHRONIC MYELOID LEUKAEMIA IN A PATIENT PREVIOUSLY TREATED WITH RADIOTHERAPY FOR LOCALIZED RETICULUM CELL SARCOMA. (E.) Jones, C. T. A. (Christie Hosp. Manchester, England). *Brit J Radiol* 44(526):801-802, 1971.
- 2473 CHOLANGIOSARCOMA ASSOCIATED WITH THORIUM DIOXIDE (THOROTRAST): REPORT OF A CASE. (E.) Rota, A. N. (Sinai Hosp., Detroit, Mich.), H. K. Weindling and P. G. Goodman. *Mich Med* 70(25):911-915, 1971.
- 2474 HISTOLOGICAL HISTOCHEMICAL STUDY OF THE CHANGES IN THE KIDNEYS AFTER AN EXPERIMENTAL FRACTIONATED LOCAL EXPOSURE TO X-RAYS. (Ger.) Kovacs, L. (Hungarian Acad. Sci., Budapest). *Strahlentherapie* 142(3):331-339, 1971.
- 2475 CHRONIC CERVICAL AND FACIAL RADIODERMATITIS. PROPHYLAXIS AND PREVENTION OF THEIR MALIGNANT TRANSFORMATION. (Fr.) Preaux, J. (St. Louis Hosp., Paris, France) and M. Texier. *J Franc Otorhino-laryng* 20(9):1033-1035, 1971.
- 2476 ALTERATIONS IN GROWTH PROPERTIES AND VIRUS SENSITIVITY OF L-M CELLS FOLLOWING CONTINUOUS LOW-LEVEL GAMMA IRRADIATION. (E.) Gardiner, G. R. (Sch. Med., U. Michigan, Ann Arbor) and C. Shipman, Jr. *Radiat Res* 50(2):358-378, 1972.
- 2477 RADIATION-INDUCED HUMAN CHROMOSOME ABERRATIONS: II. HUMAN *IN VITRO* IRRADIATION COMPARED TO *IN VITRO* AND *IN VIVO* IRRADIATION OF MAR-MOSET LEUKOCYTES. (E.) Brewen, J. G. (Biol. Div., Oak Ridge Natl. Lab., Tenn.) and N. Gengozian. *Mutat Res* 13(4):383-391, 1971.
- 2478 AN AGENT INDUCED FROM TUMOR CELLS BY X-RAYS IRRADIATION. (E.) Nishioka, K. (Osaka U. Med. Sch., Japan). *Med J Osaka U* 21(4):265-279, 1971.
- 2479 CANCER DEVELOPED IN AN ISOLATED STOMACH AFTER A ROUX-HERZEN-YUDIN PROCEDURE, PERFORMED LONG AGO, FOR AN ARTIFICIAL ESOPHAGUS. (Rus.) Sapozhnikova, M. A. (Sklifosovsky Sci. Res. Inst., USSR). *Vop Onkol* 17(11):101-102, 1971.
- 2480 EFFECTS OF IONIZING RADIATION ON BACTERIAL DNA-MEMBRANE COMPLEXES. (E.) Cramp, W. A. (Hammersmith Hosp., London, England), D. K. Watkins and J. Collins. *Nature New Biol* 235(55):76-77, 1972.
- 2481 RADIATION CANCERS AND A-BOMB SURVIVORS. (E.) Jablon, S. (Natl. Acad. Sci., Washington, D.C.). *Lancet* (7746):375, 1972.

## See also:

- \* (Rev): 2210, 2219, 2246, 2271, 2286
- \* (Chem): 2309, 2317, 2328, 2386
- \* (Immun): 2663



2482 IS A SPECIFIC PROTEIN RESPONSIBLE FOR THE SUPERCOILING OF POLYOMA DNA? (E.)

Bourgau, P. (Univ. Sherbrooke, Quebec) and D. Bourgau-Ramoisy. *Nature* 235(5333):105-107, 1972.

The effect of puromycin, a rapid inhibitor of protein synthesis, on a protein-DNA complex isolated from the TSP 1 variant of polyoma virus was investigated. When whole mouse embryo cells which were actively replicating polyoma DNA were exposed to puromycin, incorporation of  $^3\text{H}$ -thymidine into a sodium deoxycholate-extractable protein-DNA complex was inhibited two- to tenfold as compared to material extracted from non-treated controls. The protein-DNA complex from puromycin-treated cells sedimented between the 20S (closed form) and 16S (open form) polyoma DNA markers on neutral sucrose density gradients, whereas material extracted from controls sedimented at 25S. Treatment with proteolytic enzymes or detergents changed the sedimentation profile of the control DNA to that of the 20S marker, whereas the same treatment exerted little or no change on sedimentation properties of the "puromycin" DNA, indicating that "puromycin" DNA was not bound to protein in the same manner or that the conformation of DNA differed between the treated and untreated infected cells. Since, on alkaline sucrose gradients, most of the labeled material from both preparations sedimented with the denatured 53S polyoma DNA marker, it was suggested that the "puromycin" DNA might consist mostly of covalently closed circular molecules deficient in tertiary turns. When "normal" and "puromycin" DNA's were mixed with  $^{14}\text{C}$ -labeled marker viral DNA and subjected to buoyant density gradient centrifugation in  $\text{CsCl}$  with ethidium bromide or propidium diiodide, the "normal" DNA produced two radioactive bands which coincided with marker, whereas the lower band formed by the "puromycin" DNA sedimented at a higher density than the lower marker band, indicating that the covalently closed molecules present in the "puromycin" DNA had a lower superhelix density. Results from pulse-chase experiments using  $^3\text{H}$ -thymidine followed by either cold thymidine or 5-bromodeoxyuridine provided no evidence in support of a mechanism whereby superhelical turns would be introduced in polyoma DNA independently from replication. It is concluded that puromycin may inhibit polyoma DNA synthesis by preventing synthesis of one or more proteins which affect the configuration of viral DNA.

simple cultures or in cells cocultivated with primary human embryo cell monolayers, either before or after exposure to UV light or X-ray. Nor was it possible to demonstrate focus formation of human fibroblast monolayers with filtered culture fluids from such treated cells. Cell cultures maintained for 17 months in medium containing fetal bovine serum were placed in medium containing 15% heat-inactivated fetal bovine serum, medium containing 15% heat-inactivated human fetal cord serum, or medium containing 15% heat-inactivated fetal cord serum and 20  $\mu\text{g}/\text{ml}$  5-iododeoxyuridine (5-IUDR) for three or four days. Electron microscopic examination of these cultures showed that no budding virus particles were present in the controls without 5-IUDR. However, budding particles resembling C-type oncornavirus were readily found in 1.0% of the cells in cultures containing 5-IUDR.

2484 EVIDENCE FOR A HUMAN OSTEOSARCOMA VIRUS. (E.) Pritchard, D. J. (Argonne Natl.

Lab., Illinois), C. A. Reilly, Jr. and M. P. Finkel. *Nature New Biol* 234(47):126-127, 1971.

Twelve osteosarcomas, nine fibrosarcomas and four benign bone tumors developed in Syrian hamsters inoculated at birth with cell-free extracts of human osteosarcomas. The indirect fluorescence antibody technique was used to examine sera from 24 osteosarcoma patients and 24 healthy individuals. Distinct, bright, apple-green cytoplasmic and membranous fluorescence was seen in 23 of the 24 osteosarcoma sera; 22 of the 24 normal sera were clearly negative. Five hamster sarcomas carried as s.c. transplants in hamsters inoculated at birth with human osteosarcoma cell-free extracts, one spontaneous hamster reticular tumor, and nine normal hamster tissues, were reacted with 11 of the positive human osteosarcoma sera, using the indirect immunofluorescence technique. Four of the five hamster sarcomas gave positive results with each of the 11 human osteosarcoma sera. Experimental results thus demonstrate sarcoma-specific antigen in human osteosarcomas and indicate that a human virus caused the hamster tumors.

2483 ACTIVATION IN VITRO, BY 5-IODODEOXYURIDINE, OF A LATENT VIRUS RESEMBLING C-TYPE VIRUS IN A HUMAN SARCOMA CELL LINE. (E.) Stewart, S. E. (Sch. Med., Georgetown U., Washington, D. C.), G. Kasnic, Jr., C. Draycott, W. Feller, A. Golden, E. Mitchell and T. Ben. *J Nat Cancer Inst* 48(1):273-277, 1972.

A monolayer culture was established from a biopsy specimen of an undifferentiated sarcoma of the thigh of a 38-yr-old female. Two months after the cultures were initiated, the cells which had grown out as fibroblasts suddenly transformed to epithelioid-like cells with rounded cells that piled up and were shed into the culture medium. No viruses were observed by electron microscopy in cells from the

2485 INDUCTION OF ANTINUCLEAR ANTIBODIES IN THE MOUSE BY LEUKEMOGENIC GRAFFI VIRUS.

(Fr.) Cannat, A. (Hosp. St.-Louis, Paris, France) and B. Varet. *C R Acad Sci [D] (Paris)* 273(25):2698-2700, 1971.

An abnormally high level of antinuclear antibodies detectable by immunofluorescence were induced six months after i.p. injection of 0.1 ml of a 0.1 solution of Graffi's leukemogenic virus to less than 72-hour-old hybrid mice of the F 1 strain (Balb/c x C 57 Bl/6). No such reaction occurred after six months in parental strains, but it did appear later. The experiments further disclosed that the appearance of antinuclear antibodies was dependent on genetic factors, on the viru-

lence of the virus and, to a lesser degree, on sex. The earlier appearance of this phenomenon in hybrids other than parental strains was also observed previously in the New Zealand strain of mice. Thus, these strains manifest a genetic predisposition to autoimmune diseases, suggesting that genetic factors play a greater role than environmental factors. These strains are consequently useful for studying factors suspected in the etiology of lupus erythematoses. Induction of nuclear antibodies does not seem to be related to the oncogenicity of the Graffi virus, since more than half the mice in which an abnormally high level of antinuclear antibodies appeared did not develop tumors. The parallelism between the virulence of the virus and the early appearance of antinuclear antibodies suggests that viral multiplication may act as an inducer, because of the number of cells infected, the quantity of virus produced, or the existence of replicative forms acting on DNA.

- 2486 COMBINED NEOPLASTIC EFFECTS OF VACCINIA VIRUS AND 3-METHYLCHOLANTHRENE. I. STUDIES WITH MICE OF DIFFERENT INBRED STRAINS. (E.) Duran-Reynals, M. (Albert Einstein Coll. Med., Bronx, N.Y.). *J Nat Cancer Inst* 48(1):95-104, 1972.

Female mice of eight strains were treated with various combinations of cortisone (1 mg s.c. daily for five days), vaccinia virus (inoculated i.d., alone or on the last day of cortisone treatment), and 3-methylcholanthrene (MCA) (1% solution painted daily for five days on shaved skin). Mice were of the following strains: BALB/c, C3HeB/Fe, A, C58, DBA/1, DBA/2, B10.D2 (new) and AKR. No acute skin response to vaccinia was seen in mice of any strain given vaccinia alone; mice of strains highly susceptible to MCA skin carcinogenesis (BALB/c and C3H) showed slight skin ulceration when given vaccinia and MCA. Cortisone suppressed skin resistance to vaccinia in BALB/c, C3HeB/Fe, A and C58 mice. In mice given cortisone, vaccinia and MCA (the C-V-MCA group), suppression by cortisone of skin resistance to vaccinia was significantly potentiated by MCA. In the C-V-MCA group, vaccinia induced skin lesions which evolved into neoplasia. The skin response of the different strains in the C-V-MCA group to vaccinia and MCA ranged from extreme susceptibility to both (BALB/c) to virtually complete resistance to both (AKR). Skin susceptibility to vaccinia and to MCA was low in those strains showing a high incidence of leukemia, either spontaneous (AKR and C58) or MCA-induced (DBA/1 and DBA/2). Both cortisone and MCA painting induced acute lymphocyte depletion in thymus, spleen and lymph nodes of AKR as well as BALB/c mice. Thymectomy did not render BALB/c mice susceptible to vaccinia without cortisone, but did enhance the acute skin response to vaccinia plus cortisone in BALB/c. However, thymectomy had no effect on the skin resistance of AKR mice to vaccinia infection or to MCA, with or without cortisone. It is thought that immunosuppression is a major factor in the skin susceptibility of BALB/c to vaccinia, but has no effect on the resistance of AKR mice to the virus.

- 2487 PROPERTIES OF MOUSE LEUKEMIA VIRUSES: II. ISOLATION OF VIRAL COMPONENTS. (E.) Schäfer, W. (Max-Planck Inst. Virus Res., Tübingen, Germany), J. Lange, P. J. Fischinger, H. Frank, D. P. Bolognesi and L. Pister. *Virology* 47(1):210-288, 1972.

Sephadex G-150 filtration and density gradient centrifugation of Tween-ether degraded murine leukemia virus (MuLV) yielded three viral substructures: antigens IIgs (gs-specific) and IIv (type-specific), a component called component X and antigen V (gs-interspecific). Separation of IIgs and IIv antigens was not successful with any of the methods employed; it was therefore, surmised that a single complex was formed. Use of electron microscopy showed component X to be a disk- or ringlike structure, having a diameter of about 100 Å, which could aggregate into filaments. Further studies showed it to have an electrophoretic mobility of 150,000 daltons, corresponding to the 150,000 dalton protein that was present in the total virus. Antigen V isolated from Gross virus gave an identity reaction with a component of feline leukemia virus in the Ouchterlony tests. Treatment of the murine viruses with neuraminidase and phospholipase C or with phospholipase C alone (less effective) removed MuLV-antigen 1 (gs-specific).

- 2488 STIMULATING EFFECT OF MOUSE SARCOMA VIRUS ON THE MULTIPLICATION OF NEWCASTLE DISEASE VIRUS. (E.) Peries, J. (St. Louis Hosp., Paris, France), M. Canivet, M. Olivie and M. Boiron. *J Gen Virol* 14:207-208, 1972.

In Swiss mouse embryo cells (SMEC) preinfected with 1 focus-forming unit/cell of murine sarcoma virus-Moloney (MSV-M) and infected 48 hr later with 10 embryo infectious doses/cell of Newcastle disease virus (NDV), about 100 times more NDV was produced than in normal NDV-infected cultures, suggesting that the MSV-M blocks the action of the interferon produced by NDV. Interferon production in MSV-M infected cells treated with UV-inactivated NDV was the same as that in uninfected control cells. However, cells inoculated with MSV-M and treated with inactivated NDV were not protected against the cytopathic effect of vesicular stomatitis virus. This indicated that the mechanism of interferon production was unaffected by MSV-M despite inhibition of the antiviral effect of interferon, suggesting the possibility that MSV-M improved the infective yield of NDV by decreasing the cellular sensitivity to the antiviral action of interferon.

- 2489 EVIDENCE FOR TRANSLATION OF VIRAL-SPECIFIC RNA IN CELLS OF A MOUSE MAMMARY CARCINOMA. (E.) Axel, R. (Coll. Phys. Surg., Columbia U., New York, N.Y.), J. Schlom and S. Spiegelman. *Proc Nat Acad Sci USA* 69(3):535-538, 1972.

A procedure for detection of viral-specific RNA in



a mouse mammary tumor is described.  $^3\text{H}$ -labeled DNA synthesized *in vitro* from murine mammary tumor virus RNA templates, purified from viruses found in the milk of tumor-bearing Paris RIII strain mice, was used to test for the presence of RNA homologous to viral RNA in nuclear and polysomal fractions of breast tumors from Paris RIII mice, and of normal breast tissue from lactating tumor-free C57 mice. The purified  $^3\text{H}$ -dTTP-labeled denatured DNA was annealed (0.4 M NaCl-50% formamide, 18hr. at  $37^\circ\text{C}$ ) to nuclear or polysomal RNA preparations from tumor tissue, and analyzed by  $\text{Cs}_2\text{SO}_4$  equilibrium density gradient centrifugation. Both preparations were found to contain RNA molecules complementary to the  $^3\text{H}$ -DNA from mammary tumor virus with 30-35% of  $^3\text{H}$ -DNA shifting to regions of the gradient corresponding to hybrid density. Polysomal RNA from normal mouse liver did not hybridize with mammary-tumor viral  $^3\text{H}$ -DNA nor did breast tumor polysomal RNA complex with  $^3\text{H}$ -DNA homologous to the RNA of Rauscher leukemia virus, an oncogenic agent unrelated to the mouse mammary tumor virus. Polysomal RNA from normal breast also showed no ability to hybridize to tumor virus  $^3\text{H}$ -DNA. The reaction between breast-tumor polysomal RNA and viral DNA was therefore concluded to be specific. Hybridization reactions using  $^3\text{H}$ -DNA from tumor virus and purified monosomal or polysomal RNA from mammary tumor indicated that breast-tumor RNA hybridizable to viral DNA was in the polysomes. The results implied that the oncogenic information was serving as messenger RNA to direct synthesis of proteins required for virus production, and perhaps for the maintenance of the neoplastic state as well.

- 2490 DEGRADATION OF SINGLE- AND DOUBLE-STRANDED RNA BY FROG VIRUS 3. (E.) Palese, P. (Roche Inst. Molec. Biol., Nutley, N.J.) and G. Koch. *Proc Nat Acad Sci USA* 69(3):698-701, 1972.

Ribonuclease activity was studied in preparations of frog virus 3(FV3) grown in baby hamster kidney (BHK) cells and purified by zonal and density gradient centrifugation. FV3 was able to degrade purified double-stranded  $^{32}\text{P}$ -labeled poliovirus RNA (RF-RNA) in a high salt (0.2M NaCl and 1mM  $\text{MgCl}_2$ ) assay system. With increasing incubation time the RF-RNA peak, as analyzed by sucrose density centrifugation, shifted from a value of 16S (untreated) to a value of 4S (60 min. incubation with FV3). All RNA remained acid-precipitable, indicating an endonuclease activity. The enzyme was located near the surface of the virus particle, and detergent treatment was not necessary to elicit ribonuclease activity. FV3 enzyme was most active between pH 7.5 and 9.0. No activity was seen at pH 5.0 and 6.0. Neither crude cell extracts of HeLa, BHK and mouse L-929 cells, nor purified reovirus or poliovirus assayed under high salt conditions, showed detectable ribonuclease activity against RF-RNA. Experiments indicated that lack of ribonuclease activity in uninfected cells was not due to the presence of an enzyme inhibitor. The infectivity of poliovirus RF-RNA as determined by the reduction of induced

infective centers by agar plate assay was found to decrease with time of incubation with FV3 (four to 100 mg virus) in high salt. Paradoxically, the infectivity of poliovirus RF-RNA consistently increased to as much as 146% of control after incubation with small amounts (10ng) of FV3 for 15 min. This phenomenon cannot be explained at the present time. Purified FV3 also possessed a ribonuclease activity toward single-stranded poliovirus RNA. This activity showed activity from pH 6 to 9 and did not require addition of  $\text{Mg}^{++}$ . EDTA (10mM) inhibited activity and no degradation of single-stranded RNA was found in high salt (0.2M NaCl, 10mM  $\text{MgCl}_2$ ). Extracts from both uninfected BHK and BHK cells infected with FV3 showed RNase activity against single-stranded RNA; such activity was seen in purified poliovirus or reovirus preparations. The fact that FV3 enzyme acting on single-stranded RNA was inhibited by salt and EDTA (properties not associated with known ribonucleases of animal cells) indicated that it was virus-coded or virus-induced. Treatment of FV3 with NP-40 (0.5%, 30 min.,  $37^\circ\text{C}$ ) released 50% of activity of both enzymes.

- 2491 THE INVESTIGATION OF ONCOGENIC VIRAL GENOMES IN TRANSFORMED CELLS BY NUCLEIC ACID HYBRIDIZATION. (E.) Winocour, E. (Weizmann Inst. Sci., Rehovot, Israel). *Advances Cancer Res* 14:37-70, 1971.

This report accentuates those aspects considered relevant to the understanding of the role of viral genes in transformed cells. The central issue dominating current thinking on the mechanisms of viral carcinogenesis concerns the presence, the state, and the role of viral genetic material in the transformed cell. Several lines of evidence point to the persistence of viral genes in all transformed cells and their descendants. Viral DNA sequences in the DNA of transformed cells are discussed in light of hybridization procedures utilized for the detection of viral DNA sequence, the number and state of the viral genomes, the homology between SV40 and cell DNA, and the integration of the viral DNA. With the evidence for the viral DNA established, the transcription of the viral genome with particular reference to the identification and control of viral gene activity is considered. The coding potential, quantity, location and size of viral mRNA in transformed cells are discussed. A technique for determining the proportion of the viral genome by competitive hybridization between two viral mRNA's is detailed and tables summarizing the estimates reported by several investigators are given. The difficulties which persist in establishing the common sequence in viral mRNA's from productively infected and transformed cells are presented. Recent experiments indicating a possible common basic feature in the mode of action of both DNA-containing and RNA-containing tumor viruses are presented as a challenge to tumor virologists who must face the task of formulating fundamentally similar mechanisms to account for oncogenic action.

- 2492 SOME STRUCTURAL AND ANTIGENIC PROPERTIES OF INTRACISTERNAL A PARTICLES OCCURRING IN MOUSE TUMORS. (E.) Kuff, E. L. (Nat'l. Cancer Inst., Bethesda, Md.), K. K. Lueders, H. L. Ozer and N. A. Wivel. *Proc Nat Acad Sci* 69(1):218-222, 1972.

Intracisternal A-particles isolated from several different plasma-cell tumors in BALB/c mice and from cultured neuroblastoma cells of A/J origin were analyzed, and a comparison of their structural and immunologic relationships with some oncogenic RNA viruses was made. Electrophoresis and complement-fixation and immunodiffusion assays showed that A-particles had the following properties: 1) marked structural stability of the inner particle shell; 2) a major structural protein (or group of proteins) with an apparent molecular weight of 70,000; and 3) the major protein was associated with a common antigen specificity. The data suggest that intracisternal A-particles demonstrate group-specific properties related to those of known viruses or intracellular organelles. The size spectrum of proteins represented in the intracisternal A-particles was clearly different from that seen in murine leukemia virus (MuLV) or mammary tumor virus, and the A-particle antigen was not detected in the virus samples tested. The results did not indicate that intracisternal A-particles in BALB/c myeloma cells were intracellular or incomplete forms of MuLV or that there was any production of A-particle antigen.

- 2493 ACTIVATION OF VIRUSES IN HUMAN TUMORS BY 5-IODODEOXYURIDINE AND DIMETHYL SULFOXIDE. (E.) Stewart, S. E. (Nat'l. Cancer Inst., Bethesda, Md.), G. Kasnic, Jr., C. Draycott and T. Ben. *Science* 175(4018):198-199, 1972.

Dimethyl sulfoxide (DMSO) was added to transformed rhabdomyosarcoma tissue culture cells which had been virus-activated with 5-iododeoxyuridine (IdU) to determine a) whether DMSO addition resulted in greater virus yield because of a change in the tumor cell to a more differentiated stage or b) whether DMSO addition affected cell membranes to cause greater virus replication (budding). Virus production was found to increase greatly when IdU treatment was followed by DMSO addition; more than 10% of the cells yielded a tenfold increase over that observed when the cell line was treated with IdU only. Numerous inclusions consisting of proliferating agranular endoplasmic reticulum with multiple virus particles budding from these membranes developed in many cells. DMSO medium added to cells that had not been treated with IdU did not activate virus production. A virus in a tissue culture from a metastatic bronchial node adenocarcinoma has also been demonstrated using the IdU-DMSO activation procedure. The virus resembles the one observed in the rhabdomyosarcoma in that it is a C-type particle (90-110 nm) budding from the endoplasmic reticulum. Here, however it was also found budding from the plasma membrane.

- 2494 CHLOROQUINE: PROTECTION AGAINST VIRUS-INDUCED CELL DAMAGE WITHOUT INHIBITION OF VIRUS GROWTH. (E.) Wilson, D. E. (Biol Dept., Rensselaer Polytechnic Inst., Troy, N. Y.). *J Gen Virol* 14(1):107-109, 1972.

Infection of chick embryo fibroblasts with Newcastle disease virus (NDV) was previously shown to result in degradation of cellular RNA by nucleases released from cellular lysosomes, which broke down during the course of infection. To determine whether lysosomal stabilization could prevent such degradation, infected fibroblast monolayers prelabeled with <sup>3</sup>H-uridine were treated with chloroquine (50 µg/ml) and the radioactivity in isolated RNA was compared with that from untreated infected cells. Results showed that chloroquine prevented degradation of RNA in infected cells without preventing growth of NDV. The rate of protein synthesis in infected cells as determined by the rate of incorporation of <sup>14</sup>C-leucine, began to decline at about five hr after infection and was 90% inhibited by 14 hr, whereas in the presence of chloroquine, the rate of protein synthesis in infected cells remained near normal levels. Determination of lysosomal integrity by measuring release of lysosomal enzymes into the overlay medium of infected cells showed that chloroquine did not prevent lysosomal breakdown. Thus, although chloroquine protected virus-infected cells, it did not accomplish this by the stabilization of lysosomes.

- 2495 C-TYPE VIRUS RELEASED FROM CULTURED HUMAN RHABDOMYOSARCOMA CELLS. (E.) McAllister, R. M. (U. Southern California Sch. Med., Los Angeles), M. Nicolson, M. B. Gardner, R. W. Rongey, S. Rasheed, P. S. Sarma, R. J. Huebner, M. Hatanaka, S. Oroszlan, R. V. Gilden, A. Kabigting and L. Vernon. *Nature New Biol* 235(53):3-6, 1972.

The prenatal inoculations of kittens with a line of human rhabdomyosarcoma cells (RD cells) resulted in the formation of disseminated RD cells with human karyotype (RD-114) in these animals. Although the parent RD cell line contained no detectable C-type virus particles, two of the induced brain tumors and a cell line derived from one of these tumors did contain C-type particles. Techniques used for cell culture, virus transformation assays, serological tests, RNA isolation, RNA dependent DNA polymerase assay are described in earlier reports. In reported tests on a cell line from the tumor at several passage levels, sonicated RD-114 cells failed to react in complement fixation tests with antisera to the precise-specific gs-1 antigens of feline (FeLV), murine (MuLV), hamster (HaLV), rat (RaLV) or avian C-type viruses. The possibility is raised that the virus was neither a C-type virus nor a feline C-type virus. Analyses designed to characterize the RD-114 virus included: repeated complement fixation tests done between 20 and 80 days after inoculation of virus, cell transformation studies, viral neutralization tests, enzyme activity assays, and immunodiffusion testing.



In spite of the numerous possible qualifications, this virus appears to be the most likely candidate for a human C-type virus.

- 2496 DNA POLYMERASE ACTIVITY ASSOCIATED WITH L-CELL C-TYPE VIRUSES. (E.) Tavitian, A. (St. Louis, Hosp. Paris, France) and M. Boiron. *Rev Europ Etudes Clin Biol* 16(10):1023-1025, 1971.

C-type particles purified from supernatant medium of mouse L-929 cell cultures possessed a DNA polymerase activity very similar to that observed with comparative amounts of Murine sarcoma virus-Moloney (MSV-M)-(MLV) virions isolated from the 78 A-1 strain. The polymerase reaction required  $Mg^{++}$ , all four deoxyribonucleoside triphosphates, and DNA added as template. No activity was observed with exogenous purified RNA. Addition of purified L cell RNA with purified L cell DNA, or addition of purified 70S viral RNA or poly rA:rU, stimulated polymerase activity, as compared with endogenous enzyme activity. Since the C-type RNA virus from L-929 cells has not been shown to be oncogenic either *in vivo* or *in vitro*, it was suggested that the presence of DNA polymerase in RNA virions may not correlate directly with viral leukemogenesis and may possibly be a necessary, but not the only factor required for malignancy.

- 2497 ROLE OF INTERFERON IN THE PROTECTIVE EFFECT OF THE DOUBLE-STRANDED POLYRIBONUCLEOTIDE AGAINST MURINE TUMORS INDUCED BY MOLONEY SARCOMA VIRUS. (E.) De Clercq, E. (Rega Inst. Med. Res., U. Leuven, Belgium) and P. De Somer. *J Nat Cancer Inst* 47(6):1345-1355, 1971.

NMRI mice were given single or repeated injections i.p. of polyriboinosinic acid and polyribocytidylic acid (poly rI:rC) at various times before and after i.m. challenge with Moloney murine sarcoma virus (M-MSV) to demonstrate the function of interferon in the antitumor effect of poly rI:rC. Repeated injections of poly rI:rC (250 µg/ml preparation) started one day before virus challenge and continued on alternate days thereafter to day 11 inhibited the formation of M-MSV-induced tumors. Poly rI:rC treatment begun one day after M-MSV inoculation and continued on alternate days to the 11th day was also effective in inhibiting the development of MSV tumors. Tumor formation was delayed only if a high virus inoculum ( $10^{-2}$  dilution) was used; but tumor formation was definitely suppressed with a lower virus inoculum ( $10^{-2.6}$  dilution). At ten days after M-MSV challenge ( $10^{-2}$  dilution), 18% of mice given repeated doses of poly rI:rC had developed tumors, while 85% of mice given M-MSV without poly rI:rC had developed tumors. To evaluate directly the function of interferon in the antitumor action of poly rI:rC, the effects of poly rI:rC and of exogenous interferon administration were compared. Tumor growth was markedly inhibited with single doses of poly rI:rC at 5 or 25 µg/mouse injected 12 hr before M-MSV inoculation. At 25 µg/mouse the tumor incidence was significantly reduced in animals

receiving either a  $10^{-2}$  or a  $10^{-2.6}$  dilution of M-MSV. At 5 µg/mouse, poly rI:rC was only slightly effective in mice given a  $10^{-2}$  dilution but significantly more active in animals given a  $10^{-2.6}$  dilution. Exogenous interferon inoculation (200 U, i.p.) gave an antitumor effect intermediate between the protective effects of 5 and 25 µg/mouse of poly rI:rC. Results are thought to indicate that the whole antitumor effect of a single dose of poly rI:rC, injected at 12 hr before M-MSV, is due to interferon production.

- 2498 AFFINITY CHROMATOGRAPHY OF RNA-DEPENDENT DNA-POLYMERASE FROM RNA TUMOR VIRUSES ON A SOLID PHASE IMMUNOADSORBENT. (E.) Livingston, D. M. (Natl. Cancer Inst., Bethesda, Md.), E. M. Scolnick, W. P. Parks and G. J. Todaro. *Proc Nat Acad Sci USA* 69(2):393-397, 1972.

A solid phase immunoabsorbent specific for RNA-dependent DNA polymerase was prepared by coupling rabbit anti-Rauscher murine leukemia virus (R-MuLV) polymerase to Sepharose 4B. The column quantitatively bound partially purified RNA-dependent DNA polymerase from R-MuLV and feline sarcoma-leukemia virus complex (G-FeSV) but did not bind polymerase from the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV). Yields of active R-MuLV and G-FeSV polymerase varied from 25-40%. No binding occurred to control IgG columns. From these results it is concluded that G-FeSV polymerase is immunologically related to the R-MuLV polymerase and that SR-RSV polymerase is not related to either of these. Seventy-five percent of RNA-dependent DNA polymerase activity from crude cellular extracts of murine sarcoma virus-transformed BALB/3T3 cells bound to antipolymerase columns. Yields of active polymerase were 25% of that in the control column, wash-through fractions. Practically no polymerase activity was detected in column eluates of crude extracts from non-virus producing BALB/3T3 cells when poly rA:oligo dT<sub>(12-18)</sub> was used as template. Use of poly rA:poly dT as template showed that binding of viral RNA-dependent DNA polymerase to antipolymerase columns was specific, as host cell DNA polymerase was detected only in the preparatory column washes and not in column eluates containing viral polymerase. Results from SDS-disc gel electrophoresis indicate that viral polymerase can be purified from crude cell extracts.

- 2499 INDUCTION OF MUTATIONS IN AN RNA TUMOUR VIRUS BY AN ANALOGUE OF A DNA PRECURSOR. (E.) Bader, J. P. (Natl. Cancer Inst., Bethesda, Md.) and N. R. Brown. *Nature New Biol* 234(44):11-12, 1971.

The effect of 5-bromodeoxyuridine (BrdU) on the infectivity and transforming ability of the transforming Bryan strain of Rous sarcoma virus (RSV), the non-transforming Rous-associated virus (RAV) and phenotypic mixtures, was studied in chick embryo cells. Infectivity, determined by the number of focus-

forming units, was decreased only if BrdU (25-100 µg/ml) was present during the first 12 hr immediately after exposure of the cells to virus. RSV yields from BrdU-treated cultures showed a 1.3- to 1.9-fold increase in infectivity at low temperatures (36°C) and a slight decrease at high temperatures (40.5°C), as compared to controls, indicating that a significant proportion of the virions produced by BrdU-treated cells contained a genetic defect(s) which caused a temperature-sensitivity for the transformation process. Established virus-producing cells treated with BrdU did not produce such temperature-sensitive populations, nor did cells pretreated with BrdU before infection. With increasing time after infection of cells and exposure to BrdU, the proportion of the general virion population consisting of temperature-sensitive transforming virions decreased. Attempts to isolate RSV defective in the genomic regions responsible for transformation resulted in cells which produced both RAV and temperature-sensitive RSV. Of 119 transformed clones isolated from foci induced by BrdU-RSV, 20 yielded RSV which failed to induce transformation at 40.5°C. Seven of these latter clones produced RSV which transformed cells only at 36°C; the other 13 clones produced virus which did alter cell morphology at 40.5°C, but only when infection was made using high multiplicities per cell. These morphological changes were atypical of the transformation characteristic of the Bryan "high titer" strain of RSV. No temperature-sensitive RSV was found in clonal isolates of control RSV-induced foci. The production of mutations in RSV, an RNA tumor virus, by BrdU demonstrated that the replicative form of the virus, at least the region determining transformation, was DNA.

- 2500 RNA TUMOR-VIRUS ANTIGEN EXPRESSION IN CHEMICALLY INDUCED TUMORS: VIRUS-GENOME-SPECIFIED COMMON ANTIGENS DETECTED BY COMPLEMENT FIXATION IN MOUSE TUMORS INDUCED BY 3-METHYLCHOLANTHRENE. (E.) Whitmire, C. E. (Microbiol. Assoc., Inc., Bethesda, Md.), R. A. Salerno, L. S. Rabstein, R. J. Huebner and H. C. Turner. *J Nat Cancer Inst* 47(6):1255-1265, 1971.

Mice of 16 strains were injected with 150 µg 3-methylcholanthrene (MCA) and examined for eight months for tumor development. When tumors had developed, mice were killed, tumors, spleens and normal muscles were removed, and extracts were prepared. Extracts were tested for murine C-type RNA virus complement-fixing (CF) group-specific (gs) antigens using microtiter CF tests with pools of sera taken from rats with transplanted sarcomas induced by Moloney murine sarcoma virus. Most tumors which developed were s.c. sarcomas of mesenchymal origin. When tested with a broadly reactive serum pool, 87-100% of tumor extracts reacted positively. Extracts of normal mesenchymal tissues from tumor-bearing and tumor-free mice were negative in the CF test for antigens. This indicated that during MCA induction of tumors, tumorous mesenchymal tissue acquired new gs antigen

expression. The concurrent activation or derepression of expression of viral or virus-related antigens in tumors suggests that oncogenes of C-type RNA virus genomes serves as specific determinants of induced cancers. It is suggested that MCA's carcinogenic action is achieved by derepressing endogenous RNA tumor virus oncogenes which are present in all mouse cells.

- 2501 THE GENOME OF RNA TUMOR VIRUSES CONTAINS POLYADENYLIC ACID SEQUENCES. (E.)

Green, M. (Inst. Molecular Virology, St. Louis U. Sch. Med., Missouri) and M. Cartas. *Proc Nat Acad Sci USA* 69(4):791-794, 1972.

<sup>32</sup>P-labeled 70S RNA extracted from purified murine sarcoma virus (MSV), Moloney (M) and Harvey (H) isolates, and avian myeloblastosis virus (AMV) bound efficiently (62-97%) to Millipore filters in buffer with high-salt concentration but not in low-salt buffer (3-10%). 34-38% of native 70S RNA and 16-20% of the heat-denatured 70S RNA from MSV-M and MSV-H were bound to poly(U) filters. MSV-M 70S RNA showed partial resistance to digestion by pancreatic RNase. These results imply that poly(A)-sequences are present in the genomes of RNA tumor viruses. Digestion of MSV-M 70S RNA by pancreatic RNase yielded poly(A) sequences which contained 91% adenylic acid as identified by paper electrophoresis. These poly(A) sequences sedimented as a relatively homogeneous peak in sucrose density gradients as 4 to 5S material, but had a polyacrylamide gel electrophoretic mobility of 6 to 7S. The molecular wt of poly(A) of MSV-M 70S RNA was estimated to be between 30,000 and 60,000 (100-200 nucleotides). Calculations indicate that from one to eight poly(A) segments may be present in each viral genome. It is concluded that poly(A) may play a role in the initiation of viral DNA or RNA synthesis, in protein maturation, or in the assembly of the viral genome.

- 2502 NUCLEASE ACTIVITY OF LARGE RNA VIRUSES. (E.)

Rosenbergova, M. (Slovak Acad. Sci., Bratislava, Czechoslovakia) and S. Pristasova. *Acta Virol* 16:1-8, 1972.

The ability of purified myxo- and paramyxoviruses and avian myeloblastosis virus (AMV), to degrade Ehrlich ascites tumor cell RNA *in vitro* was studied. Studies on the effect of temperature on RNA degradation by myxoviruses (A2/Singapore and fowl plaque virus), paramyxoviruses (Sendai and Newcastle disease virus), and AMV (strain BAI-A) showed very little degradation below 30°C. Maximum ribonuclease activity was observed after 45 min incubation at 60°C, with hydrolysis of 90-100% of RNA. Ability of myxo- and paramyxoviruses to degrade poly C and RNA was not affected by preheating to 50°C for 45 min, and preheating at 60°C decreased activity by only 20%. Pretreatment of myxoviruses at 50 and 60°C decreased ability to degrade poly A by 20 and 70%, resp. Myxoviruses differed markedly from paramyxoviruses in their ability to cleave synthetic polynucleotides. Whereas myxoviruses



could degrade essentially 100% of poly C and poly A and 70% of poly U and poly I, paramyxoviruses degraded only poly C completely; only 30% of poly U was degraded and poly A or poly I remained practically intact. AMV completely degraded poly C but had no effect on poly A. Ability of influenza A2 virus to degrade poly C paralleled its ability to degrade RNA. A deoxyribonuclease activity was detected in the myxoviruses: A2/Singapore virus degraded 50% of heat-denatured DNA at 55°C in 45 min and degraded only 20% of native DNA under these conditions. Under the same conditions, Sendai virus had no effect on either denatured or native DNA.

- 2503      TEMPLATE PREFERENCE OF POLYMERASES AND ITS RELEVANCE TO ONCOGENIC RNA VIRUS REPLICATION: (E.) Erhan, S. (Sch. Vet. Med., U. Pennsylvania, Philadelphia), E. A. Franko and R. J. Rutman. *Experientia* 27(9):1077-1079, 1971.

Evidence is presented showing that template preference of an enzyme is variable. Calf thymus DNA polymerase (CT-DPe) has been previously reported as having an absolute preference for single stranded DNA (ss-DNA) template. In these experiments it was demonstrated that when the enzyme was first obtained and tested it did show a definite preference for DNA with up to 20% of the DNA activity being noted when double stranded DNA (ds-DNA) was the template. After one year of storage at -17°C (without treatment) a change of template preference to ds-DNA occurred. This changed could be reversed by treating the enzyme with urea or EDTA. Using *M. luteus* DPe the template preference could be shifted to a more efficient use of ss-DNA by dialyzing with EDTA. This could be reversed back to ds-DNA preference by keeping the dialyzed enzyme in 1 M sucrose, 1 M NaCl or 50% glycerol. These results indicate that the CT-DPe with ss-DNA preference might be an isolation artifact. Hence, interpreting results based on a property which can be manipulated or show spontaneous change should be done with caution.

- 2504      BIS-DEAE-FLUORENONE: A SPECIFIC INHIBITOR OF DNA POLYMERASES FROM RNA TUMOR VIRUSES. (E.) Chandra, P. (Inst. Therap. Biochem., U. Frankfurt, Germany), F. Zunino and A. Götze. *FEBS Letters* 22(2):161-164, 1972.

The effect of bis-DEAE-fluorenone (DEAE-F) on the polymerases from mammalian RNA tumor viruses, FLV (Friend) and MSV (Moloney) is reported. DEAE-F added to an assay mixture inhibited DNA polymerase activity in MSV and FLV. At low concentrations of DEAE-F (5 µg/0.25 ml reaction mixture), the MSV system was more sensitive than FLV resp. Higher concentrations produced about the same inhibition for both viral enzymes. The reaction catalyzed by poly(dA-dT) was most sensitive to DEAE-F. At 5 µg/reaction mixture of DEAE-F more than 80% inhibition of <sup>3</sup>H-TMP incorporation was seen. Reactions catalyzed by poly(rA.dT) and poly rA.(dT)<sub>12</sub> were not inhibited by this concentration of DEAE-F. At higher concentra-

tions, however, reactions catalyzed by both polynucleotides were very sensitive to DEAE-F, with that catalyzed by poly rA.(dT)<sub>12</sub> being twice as sensitive as that catalyzed by poly(rA.dT). DEAE-F strongly stimulated incorporation of <sup>3</sup>H-dGMP into DNA in the reaction catalyzed by poly(dI.dC). Regardless of the template used, the MSV system was more sensitive than the FLV system to DEAE-F inhibition. The poly(dA-dT) catalyzed reaction was totally inhibited with 5 µg DEAE-F. No difference in sensitivity between MSV and FLV was seen when poly(rA.dT) was used to catalyze the polymerase. The poly rA.(dT)<sub>12</sub> catalyzed reaction in MSV was twice as sensitive toward all concentrations of DEAE-F as the one in FLV. Levels of DEAE-F that inhibit viral (both MSV and FLV) DNA polymerase activity, poly(dA-dT)-dependent incorporation of TMP, more than 90% show no inhibition of DNA-dependent RNA synthesis in an *E. coli* system.

- 2505      CYTOPLASMIC DNA SYNTHESIS INDUCED BY RNA TUMOR VIRUSES. (E.) Hatanaka, M. (Flow Labs., Inc., Rockville, Md.), T. Kakefuda, R. V. Gilden and E. A. O. Callan. *Proc Nat Acad Sci USA* 68(8):1844-1847, 1971.

Results of experiments designed to show that RNA tumor virus infection leads to nonmitochondrial cytoplasmic DNA synthesis are presented. The Harvey strain of murine sarcoma virus (H-MSV), the Rauscher pseudotype of MSV (MSV(RLV)), and Rauscher leukemia virus (RLV) were used to infect BALB/3T3 mouse embryo fibroblasts. Autoradiographic examination of infected cells showed cytoplasmic DNA synthesis shortly after infection; this was seen clearly with both light and electron microscope autoradiography. No apparent differences were seen between H-MSV-, MSV(RLV)-, or RLV-infected cells. Cytoplasmic grain density was eight times higher in infected than in uninfected or UV-inactivated cells. Using electron microscopy it was seen that the number of grains on the mitochondria or intracytoplasmic vesicles was similar in both control and infected cells. However, a large number of grains was found in the cytoplasmic matrix of infected cells. Experimental results thus showed that new DNA synthesis occurs rapidly after virus infection. It is postulated that this may represent a true intermediate in the replication cycle.

- 2506      GENES OTHER THAN H-2 DETERMINING SUSCEPTIBILITY TO FRIEND VIRUS. (E.) Steeves, R. A. (Roswell Park Mem. Inst., Buffalo, N.Y.). *Transplantation Proc* 3(3):1237-1238, 1971.

C57BL mice are known to be resistant to Friend virus-induced splenomegaly and spleen focus formation. Recent studies have shown that genes at two unlinked loci, called *Fv-1* and *Fv-2*, are mainly responsible for this resistance. It was found that the as yet unmapped *Fv-1* gene seems to control the relative susceptibility of mice to all murine leukemia viruses. The *Fv-1<sup>b</sup>* allele conferred reciprocal susceptibility and resistance. It is postulated that the *Fv-1<sup>b</sup>*

gene may inhibit an N-tropic helper virus which is found in a high titer as a lymphatic leukemia virus in stocks of Friend virus complex.

- 2507 MALIGNANT TRANSFORMATION AND ERYTHROID DIFFERENTIATION BY POLYCYTHAEMIA-INDUCING FRIEND VIRUS. (E.) Tambourin, P. (Fac. Sci., Orsay, France) and F. Wendling. *Nature New Biol* 234(51): 230-233, 1971.

Early events in the induction of the erythropoietin (EP)-independent erythropoietic differentiation, and the nature of target cells, in Friend virus-induced leukemia are studied. The results showed that approximately 30 hr postinfection with a polycythemia-inducing Friend's virus (FVP), hypertransfused plethoric (HP) mice had millions of hyperbasophilic cells in the red pulp of the spleen, which were thought to be produced *in situ* by transformation or by migration of unidentified cells. This reaction was accompanied by hemoglobin synthesis and erythropoietic differentiation. In experiments to determine the target cell for oncogenicity the EP and virus erythropoietic function interactions were studied. The results of  $^{59}\text{Fe}$  blood uptake in HP mice injected with the virus and EP (17% after EP, 7% after FVP and 15% after FVP followed by EP) suggest that these two erythropoietic functions are not independent, since the uptake would be additive if they were. Two possible explanations for this are: that the EP and FVP target cells are different cells and that the virus reduced or delayed erythroblastic maturation due to EP, or that the EP and virus have the same target cells.

- 2508 ACCELERATED TRANSFORMATION BY POLYOMA VIRUS IN RAT EMBRYO CELLS INFECTED WITH RAUSCHER LEUKEMIA VIRUS. (E.) Rhim, J. S. (Microbiological Associates, Inc., Bethesda, Md.), C. R. Lengel, K. K. Takemoto and R. J. Huebner. *Proc Soc Exp Biol Med* 138(1):308-311, 1971.

Transformation by polyoma virus of Rauscher leukemia virus (RLV)-infected rat embryo (RE) and uninfected RE cells was studied. Eight to ten days after infection with polyoma virus, small, densely opaque foci consisting of cells piled up in a multilayered, irregular array were seen in the RLV-infected RE cultures. In the RLV-uninfected RE cells foci were first observed 11 to 13 days after polyoma virus infection. Transformation efficiency of polyoma virus in the RLV-infected RE cells determined by the number of foci after 21 days of infection was 20 to 30 times greater than that in the RLV-uninfected RE cells. Transformation of both the polyoma-infected RE lines was confirmed by their specific reaction in complement-fixation tests with polyoma T specific antisera; and the polyoma T antigen was also detected by the fluorescent antibody test.

- 2509 STUDIES ON THE SUSCEPTIBILITY OF C57BL/6 MICE TO RAUSCHER VIRUS: II. MULTIPLICATION OF RAUSCHER VIRUS IN C57BL/6 CELLS *IN VIVO*

AND *IN VITRO*. (E.) Ishimoto, A. (Aichi Cancer Ctr., Nagoya, Japan), Y. Ito and M. Maeda. *J Nat Cancer Inst* 47(6):1299-1308, 1971.

Twelve spleens from C57BL/6 mice were removed and minced and fragments were established in TD40 flasks. Six flasks were inoculated with 1 ml of Rauscher leukemia virus preparation, and six remained uninoculated. Two wk after virus inoculation, cells in three of six virus-treated flasks began to proliferate. Three spleen cell lines which produced Rauscher virus were established from virus infected spleen cell cultures. Tissue culture fluids from the cultures were injected into weanling and newborn mice. Inoculated mice developed erythroblastosis and lymphoma. The maximum dilution of tissue culture fluid from the three cell lines to cause erythroblastosis in SMA or BALB/c mice was always over  $10^{-2}$ , and attained  $10^{-3}$ . The infectivity titer of virus propagated in C57BL/6 mouse cells seemed almost the same as that of virus propagated in BALB/c cells. In *in vivo* experiments, eight groups of C57BL/6 mice were inoculated i.p. with 1 ml Rauscher virus stock; mice were killed 7, 14, 20, 28, 30 or 120 days later and the presence of erythroblastosis-inducing Rauscher virus was demonstrated in spleens by injecting SMA mice with spleen material from infected C57BL/6 mice. Propagation of virus sufficient to induce erythroblastosis was seen in spleens of seven mice killed 7, 14 and 28 days after virus inoculation. Propagation of Rauscher virus *in vivo* in C57BL/6 mice was lower than that in BALB/c mice. The influence of Rauscher virus on the platelet count of BALB/c, SMA and C57BL/6 mice was studied. Rauscher virus caused significant thrombocytopenia in BALB/c and SMA mice, but caused little thrombocytopenia in C57BL/6 mice.

- 2510 INHIBITION OF THE DNA POLYMERASE OF RAUSCHER LEUKEMIA VIRUS BY SINGLE-STRANDED POLYRIBONUCLEOTIDES. (E.) Tuominen, F. W. (Oak Ridge Natl. Lab., Tenn.) and F. T. Kenney. *Proc Nat Acad Sci USA* 68(9):2198-2202, 1971.

The DNA polymerase of Rauscher murine leukemia virus is strongly and specifically inhibited by nontemplate, single-stranded polyribonucleotides with either the resident viral RNA, native calf thymus DNA, or poly[d(A-T)] as templates. These inhibitory homopolymers are apparently bound to the template site of the polymerase, since they interact competitively with the template. The strength of the inhibition depends on the particular homopolymer used: poly(U) > poly(G) >> poly(A) > poly(C). The  $K_i$  for poly(U) was 0.08  $\mu\text{g/ml}$ , which represents an apparent affinity six times greater than that observed for viral RNA. No such inhibition was observed with a highly purified DNA polymerase from mouse embryos or the *Escherichia coli* enzyme.

- 2511 EPSTEIN-BARR VIRUS AND INFLAMMATORY BOWEL DISEASE. (E.) Grotzky, H. W. (Mount Sinai Sch. Med., City U. New York, N.Y.), Y. Hirschaut, C.



Sorokin, D. Sachar, H. D. Janowitz and P. R. Glade. *Experientia* 27(12):1474-1475, 1971.

The incidence and distribution of antibody to Epstein-Barr virus (EBV) were determined by immunofluorescence in serum specimens from 93 normal individuals, 32 patients with Crohn's disease (granulomatous ileitis and colitis) and 17 patients with ulcerative colitis. No apparent differences were seen in overall incidence of anti-EBV antibody in these three groups of patients. Antibody titers of 1:640 or greater were found in 24% of the normal sera, 3% of Crohn's disease titers, and 11% of the ulcerative colitis sera, but these differences were not significant. Incidence and distribution of anti-EBV antibody had no relationship to sex. The percentage of individuals in all groups with positive antibody titers increased with age and the length of time that disease was present.

2512 ACTIVATION OF EPSTEIN-BARR VIRUS BY 5-BROMODEOXYURIDINE IN "VIRUS-FREE" HUMAN CELLS. (E.) Gerber, P. (Nat'l. Inst. Hlth, Bethesda, Md.). *Proc Nat Acad Sci* 69(1):83-85, 1972.

Results of a study to develop 5-bromodeoxyuridine (BrdU)-resistant lymphoid cell lines that are EB (Epstein-Barr) virus-negative for cell fusion experiments are presented. NC37, NHDL3 and Raji human lymphoid virus-free cells were cultured and treated with BrdU, resulting in the appearance of immunofluorescence-positive cells. Untreated controls contained no cells with detectable EB virus antigens. Human sera free of detectable antibodies to EB virus, but positive for antibodies to herpes simplex or cytomegalovirus failed to react with BrdU-treated cells. Antigen-positive cells were first seen three to four days after BrdU treatment and had a maximum amount of antigen (5 to 8% antigen-positive cells) after seven to ten days. It is suggested that the entire viral genome may persist in some of the "virus-free" human lymphoid cells.

2513 ENDONUCLEASE ACTIVITY ASSOCIATED WITH PURIFIED SIMIAN VIRUS 40 VIRIONS. (E.) Kaplan, J. C. (Harvard Med. Sch., Boston, Mass.), S. M. Wilbert and P. H. Black. *J Virol* 9(5):800-803, 1972.

Endonuclease activity of purified SV40 virions was assayed by the conversion of  $^3\text{H}$ -labeled form I (double-stranded, closed, circular) SV40 DNA to a nicked form. Alkaline sucrose density centrifugation revealed that the conversion product sedimented as a sharp peak, indicating that random breakage of form I DNA by the nuclease did not occur. The endonuclease activity was dependent on magnesium ion and was completely inactivated by addition of 0.2 M EDTA to the reaction mixture or by preheating of purified virus at 80°C for ten min. Maximum enzyme activity was observed at pH 6.7-7.1 in Tris-hydrochloride buffer. Reaction rate was linear up to 15 min, at which time 49% of form I DNA was converted to a nicked form. By

120 min 97% conversion occurred. The electrophoretic pattern of SV40 protein purified by two different procedures resembled patterns described in previous publications and indicated the absence of detectable contaminating host-cell protein.

2514 CONTACT-INHIBITED REVERTANT CELL LINES ISOLATED FROM SIMIAN VIRUS 40-TRANSFORMED CELLS. III. CONCANAVALIN A-SELECTED REVERTANT CELLS. (E.) Culp, L. A. (Harvard Med. Sch., Cambridge, Mass.) and P. H. Black. *J Virol* 9(4):611-620, 1972.

Four revertant clones were isolated from SV40-transformed Balb/c 3T3 (SVT2) cell cultures grown in the presence of concanavalin A (con A). The revertant cells resembled normal Balb/c 3T3 cells in that they maintained a flat morphology in either subconfluent or confluent cultures, formed monolayers, and grew to similar saturation densities. The SV40-specific T antigen was detected in more than 90% of the nuclei in SVT2 cultures and in all four revertant clones, by indirect immunofluorescence staining. All four revertant clones yielded infectious virus after fusion with a permissive monkey kidney cell line mediated by inactivated Sendai virus. Three of the revertant clones had a high sialic acid content similar to that of Balb/c 3T3 cells and not to that of SVT2 cells. The consistently low sialic acid content in the fourth revertant clone was associated with a very high propensity of this clone to "revert" to spindle-shaped cells which formed multilayers. Confluent or subconfluent SVT2 and revertant clones produced about twice as much collagen as did Balb/c 3T3 cells. The revertant clones contained approximately twice the number of chromosomes (90-99) as did the parental SVT2 cells; however, the qualitative cytogenetic characteristics of the SVT2 and the revertant cells were similar.

2515 ACTIVATION OF LEUKEMIA VIRUSES BY GRAFT-VERSUS-HOST AND MIXED LYMPHOCYTE REACTIONS IN VITRO. (E.) Hirsch, M. S. (Harvard Med. Sch., Boston, Mass.), S. M. Phillips, C. Solnik, P. H. Black, R. S. Schwartz and C. B. Carpenter. *Proc Nat Acad Sci USA* 69(5):1069-1072, 1972.

CAF<sub>1</sub> mice were given four weekly i.p. injections of  $50 \times 10^6$  viable spleen cells from six wk old male BALB/c mice. Lymphocyte suspensions were prepared from minced spleens of inoculated mice (two to seven day cultures), and lymphocyte cultures were tested for presence of leukemia virus by a mixed-culture cytopathogenicity assay. Cultures of spleen cells from CAF<sub>1</sub> and BALB/c mice not inoculated with spleen cells were negative for virus in 15 of 16 trials. However, spleen cells from CAF<sub>1</sub> mice given BALB/c spleen cells were positive for leukemia virus in ten of 11 trials; virus titers ranged from  $10^{1.2}$  to  $> 10^{3.2}$  50% tissue culture infectious doses per ml. Three to seven day cultures of mixtures of BALB/c and CAF<sub>1</sub> spleen cells were positive for leukemia

viruses in seven of 11 trials. Phytohemagglutinin induced the transformation of lymphocytes in cultures of CAF<sub>1</sub> or BALB/c spleen cells, but this transformation did not activate leukemia viruses. It was thought that mixed lymphocyte cultures *in vitro*, like graft-versus-host reactions *in vivo*, can activate leukemia viruses which are normally present in a repressed form. The increased incidence of neoplasms in recipients of renal allografts -- commonly attributed to immunosuppression -- may in fact be due to activation of leukemia viruses during overt or subtle reactions in the recipients.

2516 EPSTEIN-BARR VIRUS (EBV)-ASSOCIATED ANTIBODY PATTERNS IN MALIGNANT LYMPHOMA AND LEUKEMIA: II. CHRONIC LYMPHOCYTIC LEUKEMIA AND LYMPHOCYTIC LYMPHOMA. (E.) Johansson, B. (Karolinska Inst., Stockholm, Sweden), G. Klein, W. Henle and G. Henle. *Int J Cancer* 8:475-486, 1971.

Indirect immunofluorescence and the blocking test of direct membrane immunofluorescence, resp., were used to titrate sera from Swedish patients for antibodies to Epstein-Barr virus (EBV) capsid antigen (VCA) and to EBV-determined cell membrane antigens. Sera were examined from 59 patients with chronic lymphocytic leukemia (CLL), 23 patients with lymphocytic lymphoma (LL), and 47 donors without known malignant or EBV-related disease (controls). Forty-five percent of CLL sera had a high anti-VCA titer (geometric mean = 1:79), and 57% of CLL sera had high blocking indices (arithmetic mean = 0.50). These values were comparable to corresponding values in controls. Fifty-seven percent of LL sera had high anti-VCA titers (mean = 1:130) and 75% had high blocking indices (mean = 0.56). These values were significantly higher than corresponding values in controls. The highest EBV-related serological reactivities were found among patients with poorly differentiated LL (mean anti-VCA titer = 1:197 and mean blocking index = 0.62). The highly reactive LL sera showed anti-VCA titers and blocking indices similar to those seen in patients with other EBV-related conditions, including Hodgkin's disease, nasopharyngeal carcinoma and Burkitt's lymphoma.

2517 PERSISTENCE OF A REPRESSED EPSTEIN-BARR VIRUS GENOME IN BURKITT LYMPHOMA CELLS MADE RESISTANT TO 5-BROMODEOXYURIDINE. (E.) Hamper, B. (Natl. Cancer Inst., Bethesda, Md.), J. G. Derge, L. M. Martos and J. L. Walker. *Proc Nat Acad Sci USA* 68(12):3185-3189, 1971.

The human lymphoblastoid cell line P3HR-1 that is Epstein-Barr (EB) virus-positive was made resistant to 100 mg/ml of 5-bromodeoxyuridine (BU). Immunofluorescence and electron microscopic studies of these [P3HR-1(BU)] cells when grown in the presence of BU led to the conclusion that EB virus-associated antigens, but not virus particles, were produced in these cells and that EB virus particles appeared four days

after removal of BU. Immunofluorescence studies and autoradiography revealed an association between residual <sup>3</sup>H-thymidine incorporation and EB virus production in the BU-treated cells. However, no such correlation was seen in P3HR-1 cells. DNA synthesis preceded appearance of EB viral antigen by several days. DNA from WI-38 human lung fibroblasts was labelled with <sup>3</sup>H-thymidine and DNA from P3HR-1 and P3HR-1(BU) cells was double-labelled with <sup>14</sup>C-adenosine and <sup>3</sup>H-thymidine and characterized by CsCl density gradient centrifugation. <sup>3</sup>H-labelled DNA from WI-38 cells and <sup>14</sup>C- and <sup>3</sup>H-labelled DNA from P3HR-1 cells banded at a density of 1.69 g/cm<sup>3</sup>, the density of human DNA. The double-labelled DNA from P3HR-1(BU) cells banded at two peaks, a major one at 1.69 g/cm<sup>3</sup> and a minor one at 1.71 g/cm<sup>3</sup>. From the <sup>14</sup>C-to-<sup>3</sup>H ratios of the peaks it was concluded that DNA synthesis of P3HR-1 cells used both deoxythymidine kinase (dTK)-positive and dTK-negative pathways, that cellular DNA synthesis in P3HR-1(BU) cells used either dTK-negative pathways alone, or both dTK-positive and negative pathways, and that EB virus DNA (1.71 g/cm<sup>3</sup>) was formed only in the cells with the dTK-positive pathway. It is concluded that a repressed EB virus genome persists in the P3HR-1(BU) cells that do not contain dTK, with activation of the viral genome being accompanied by productive infection and the appearance of enzyme and that dTK activity in P3HR-1(BU) cells could be used as a marker for viral genome expression.

2518 POLYPEPTIDES OF AVIAN RNA TUMOR VIRUSES: V. ANALYSIS OF THE VIRUS CORE. (E.) Bolognesi, D. P. (Max-Planck Inst., Tübingen, Germany), H. Gelderblom, H. Bauer, K. Mölling and G. Hüper. *Virology* 47:567-578, 1972.

Avian myeloblastosis virus (AMV) was disrupted with NP40 and DTT in the presence of RNase inhibitors. Viral cores were isolated by treating the disrupted virus with ether, centrifuging, removing the ether and centrifuging the aqueous phase of the first centrifuging on a sucrose density gradient. Virus cores had a clear 30Å-thick membrane surrounding a poorly defined inner component (800Å-thick). RNA of cores was analyzed in sucrose gradients. Core RNA consisted essentially of 62S high molecular wt RNA (thought to be the viral genome). Only 2% of core RNA was 4-5S RNA, while 25% of RNA from whole AMV was 4-5S RNA. One major polypeptide, of molecular wt 28,000 daltons, was associated with the AMV core. This polypeptide had the properties of the avian RNA tumor virus group-specific (gs) antigen. A 30,000 dalton molecular wt component was also seen in AMV cores. Evidence for the presence of RNA- and DNA-dependent DNA polymerase in cores was also seen. Treatment of cores with various enzymes and examination under the electron microscope indicated that lipid and protein were required for core integrity. When core preparations were applied to chick embryo fibroblasts large quantities of gs antigen appeared in supernatants after two cell passages. Cores were thought to be biologically active and to induce production of virus particles. This suggestion was confirmed by analysis of <sup>32</sup>P-labeled chick cells which had been exposed to AMV cores and



extracted for RNA. The characteristic AMV high molecular wt RNA was found in all and only in those cultures demonstrating AMV gs antigen.

- 2519 ASSOCIATION OF VIRAL REVERSE TRANSCRIPTASE WITH AN ENZYME DEGRADING THE RNA MOIETY OF RNA-DNA HYBRIDS. (E.) Mölling, K. (Max-Planck Inst. Virus Studies, Tübingen, Germany), D. P. Bolognesi, H. Bauer, W. Büsen, H. W. Plassmann and P. Hausen. *Nature New Biol* 234(51):240-243, 1971.

Avian myeloblastosis virus (AMV) particles were assayed for activity of RNA- and DNA-dependent DNA polymerases and RNAase H (an enzyme which specifically degrades the RNA moiety of RNA-DNA hybrids). When aliquots of AMV lysate, obtained by disruption of AMV particles with Nonidet P-40, were added to a standard RNAase H assay, a linear relationship was found between the amount of disrupted AMV added to the assay and the amount of RNA digested from a hybrid of  $^3\text{H}$ -RNA synthesized on a calf thymus DNA template. Fractions of purified lysates separated by density- and velocity gradient centrifugation showed identical distributions of RNAase H and DNA polymerizing activities. All three enzymes also eluted from DEAE-Sephadex columns at 0.075 M NaCl with no separation of activities, and no nuclease activities digesting single-stranded RNA were detectable in this region of the gradient; these results suggest that all three enzymes are contained in a single complex. RNAase H was more stable than DNA polymerase when stored two wk at  $4^\circ\text{C}$ . The three enzymes exhibited different requirements for divalent cations. DNA polymerase activity on a high-molecular-weight viral RNA template was stimulated threefold by the addition of 2 mM  $\text{Mn}^{++}$ ; with DNA as a template, however,  $\text{Mn}^{++}$  strongly inhibited polymerase activity. RNAase H activity required either  $\text{Mg}^{++}$  or  $\text{Mn}^{++}$  for optimal activity. All three enzymes showed equal sensitivity to inhibition by a rifampicin derivative and, to a lesser degree, by streptovaricin. Simultaneous analysis of RNAase H and DNA polymerase activities by a double-labelling technique indicated that both enzymes acted concurrently and that RNA degradation depended on synthesis of DNA. The finding that considerably more RNA was digested than was to be expected from the amount of DNA synthesized was unexplained. It is suggested that the viral enzyme complex may direct synthesis of DNA from a viral RNA template, degrade the viral RNA from the resulting RNA-DNA complex, and then direct synthesis of DNA from the newly synthesized DNA template, thus playing a key role in virus replication.

- 2520 WIDESPREAD PRESENCE, IN CHICKENS, OF DNA COMPLEMENTARY TO THE RNA GENOME OF AVIAN LEUKOSIS VIRUSES. (E.) Baluda, M. A. (U. California Sch. Med., Los Angeles). *Proc Nat Acad Sci USA* 69(3):576-580, 1972.

DNA-RNA hybridization experiments were used to test for the presence of DNA complementary to RNA of avian myeloblastosis virus (AMV) in normal and in

Rous sarcoma virus (RSV) or AMV-BALs strain-infected adult and embryonic chick, mouse and rat cells and in leukemic chick myeloblasts. DNA complementary to  $^3\text{H}$ -labeled 71S AMV-RNA was present in RSV-transformed chick embryos, in leukemic myeloblasts from leukemic K-137 chicks, in B-77 avian sarcoma virus-transformed rat embryonic fibroblasts, and in normal SPF-K-137 chick embryos. DNA from leukemic chick myeloblasts hybridized with 1.7 times more AMV-RNA, and DNA from RSV-transformed chick embryo fibroblasts hybridized with six times more AMV-RNA, than did DNA from uninfected control cells. Under saturation conditions, the ratio of AMV-RNA hybridized by leukemic DNA to that hybridized by normal DNA was  $1.54 \pm 0.065$ . Calculations showed that leukemic DNA contained 4.95 viral DNA equivalents per leukemic cell and that normal DNA contained 3.2 equivalents per normal cell. Apparently normal K-137 strain chick embryos contained a mean of 3.2 viral genome equivalents per cell. Other normal non-virus-producing chick embryos contained as much as 3.5 viral genome equivalents per cell. Embryos from SPF-K-137 strain, which were free of AMV groups A and B and which developed 40% fewer spontaneous leukotic tumors than the original strain, contained an average of 2.1 (1.7 to 2.7) viral DNA equivalents per cell. By contrast, viral DNA in different K-137 leukemic chicks varied from 3.9 to 6.7 equivalents (mean of 5.8). The only SPF-K-137 chick tested contained 13.1 viral DNA equivalents per cell. No correlation was found between the expression of avian leukemia virus group-specific (gs) antigen and cellular concentration of viral DNA as both gs-antigen-negative embryos and their gs-antigen-positive siblings contained equivalent amounts of viral DNA. Morphological transformation was not required for an increase in cellular viral DNA concentration since infection of K-137 cells with AMV or RSV increased viral DNA concentration whether or not the cells were transformed.

- 2521 COMPARATIVE MORPHOLOGY OF AVIAN AND MURINE LEUKEMIA VIRUSES. (E.) Feller, U. (State U. New York, Upstate Med. Ctr., Syracuse), R. M. Dougherty and H. S. Di Stefano. *J Nat Cancer Inst* 47(6):1289-1298, 1971.

Avian leukosis virus (ALV), F-42 strain, from infected chick embryo fibroblast cell cultures, and the Rauscher strain of murine leukemia virus (MuLV), in the form of an infected mouse spleen homogenate, were studied by electron microscopy. It was found that fixation and preparation procedures had a marked effect on the appearance of ALV and MuLV. Those cell culture particles fixed with osmium alone were found to resemble closely those particles from intact tissues fixed with glutaraldehyde and osmium, with this appearance more closely approaching the true structure of the virion. The most important morphologic difference between ALV and MuLV was found in the structure of the mature form; no intermediate membrane was seen in mature MuLV but was distinct in mature ALV. Constant morphologic differences were seen between ALV and MuLV regardless of preparation techniques, and thus would seem to reflect true viral structural differences.

- 2522 CONDITIONAL LETHAL MUTANTS OF AVIAN SARCOMA VIRUSES II. ANALYSIS OF THE TEMPERATURE-SENSITIVE LESION IN ts 75. (E.) Katz, E. (U. Washington Sch. Med., Seattle, Washington) and P. K. Vogt. *Virology* 46(3):745-753, 1971.

Biochemical studies on the replication of the temperature-sensitive ts 75 mutant of avian sarcoma virus B77 are reported. C/B chick embryo fibroblast cultures were infected with ts 75 incubated for 70 hr at the nonpermissive temperature of 41° C; two hr after 0.3 mM cytosine arabinoside (CA), 2 µg/ml actinomycin D (AD), or 100 µg/ml cycloheximide (CH) was added the cultures were incubated for ten hr at the permissive temperature of 35° C. CA caused no inhibition of virus growth after the shift to 35° C, AD caused a partial reduction in virus yield after 30 min and CH inhibited further growth completely. It was concluded that DNA synthesis was not required for virus production after the shift and that there was no need for DNA-dependent RNA synthesis, at least during the first 30 min after transfer to the permissive temperature. Using polyacrylamide gel electrophoresis differences were seen between the patterns of viral structural proteins synthesized at 35° C and 41° C. Reduced amounts of labelled material were found in the polypeptides of peaks 1 and 4 at 41° C as compared to 35° C. After temperature shift from 41° to 35° C these polypeptides, especially peak 1, had an increased amount of radioactivity.

- 2523 INHIBITION OF ADENOVIRUS TRANSFORMATION IN VITRO BY AAV-1. (E.) Casto, B. C. (U. Illinois Med. Ctr., Chicago) and C. R. Goodheart. *Proc Soc Exp Biol Med* 140(1):72-78, 1972.

Serially diluted adeno-associated virus type 1 (AAV-1) (0.1 ml) was added to hamster embryo cell cultures; immediately thereafter, 0.2-0.3 ml of a solution of simian adenoviruses SA7 or SV11, or human adenovirus type 12 (Ad12), was added ("challenge viruses"). Three to four wk after virus additions, transformed cell foci were counted. When SA7 was used as challenge virus, five to six plaque-inhibiting U (PIU) of AAV/cell were insufficient to cause a 50% reduction of transformed cell foci. However, two to three PIU/cell were sufficient to cause 50% inhibition when either SV11 or Ad12 was used as challenge virus. In tests using two pools of concentrated AAV, about 1.5-2 PIU of AAV/cell appeared to be necessary to achieve a 50% reduction in SV11 or Ad12 transformed cell foci, while about 7-8 PIU/cell are required to cause a 50% reduction in SA7 foci. Analysis of the dose-response data suggest that one U of AAV-1/cell is sufficient to inhibit transformation by Ad12 and SV11. Inhibition of transformation by SA7 required more than one PIU AAV-1/cell.

- 2524 TRANSCRIPTION OF THE ADENOVIRUS GENOME BY AN  $\alpha$ -AMANITINE-SENSITIVE RIBONUCLEIC ACID POLYMERASE IN HeLa CELLS. (E.) Price, R. (Dept. Biol., Massachusetts Inst. Technol., Cambridge) and S. Penman. *J Virol* 9(4):621-626, 1972.

The synthesis of adenovirus type 2 (Ad-2) RNA in virus-infected HeLa S-3 cells was studied by RNA-DNA hybridization. Approximately 14-18% of <sup>3</sup>H-labeled RNA from either whole infected HeLa cells or infected HeLa nuclei hybridized to purified Ad-2 DNA. Incubation of infected nuclei with  $\alpha$ -amanitin (0.2 µg/ml) inhibited labeling of practically all Ad-2 specific RNA, indicating that the bulk of Ad-2 DNA was transcribed by an  $\alpha$ -amanitin-sensitive polymerase. Incorporation of <sup>3</sup>H-UTP into Ad-2 specific RNA was stimulated by increasing the ammonium sulfate concentration up to 75-100 mM. This response resembled that of whole cell incorporation, which, under these conditions, was due primarily to host-cell polymerase II activity. Ad-2 transcription also resembled host-cell polymerase II in its response to manganese, which decreased with increasing manganese concentration. Characterization of Ad-2 specific RNA by sucrose density gradient centrifugation and comparison with similarly prepared polymerase II-transcribed RNA from uninfected HeLa cells showed that the principal labeled products were heterogeneous nuclear (Hn)-RNA in both cases. The Ad-2 polymerase activity measured early in infection (3-5 hr) resembled that found late in infection (16-18 hr), with Hn-RNA being the principal product.

- 2525 INHIBITION BY  $\alpha$ -AMANITIN OF ADENOVIRUS 12 REPLICATION IN HUMAN EMBRYO KIDNEY CELLS AND OF ADENOVIRUS TRANSFORMATION OF HAMSTER CELLS. (E.) Ledinko, N. (Putnam Memorial Hosp., Inst. Med. Res., Bennington, Vt.). *Nature New Biol* 233:247-248, 1971.

Experiments were performed to determine the effect of  $\alpha$ -amanitin, a specific inhibitor of the mammalian DNA-dependent RNA polymerase function, on adenovirus multiplication. Human embryo kidney primary monolayer cell cultures with 2-3 x 10<sup>6</sup> cells were infected with 20-30 plaque-forming units (pfu) of human adenovirus type 12(Ad12)/cell. With 0.25 µg or more of  $\alpha$ -amanitin/ml the final yield of Ad12 was more than 80% inhibited; virus-induced cytopathic changes were also inhibited at these concentrations. It was found that  $\alpha$ -amanitin did not significantly interfere with DNA and protein synthesis in the host cell. The effect of  $\alpha$ -amanitin on *in vitro* Ad12-transformed hamster embryo cells was also studied; these cultures were infected with 30-40 pfu Ad12/cell. As compared with foci in untreated cultures, cultures treated with  $\alpha$ -amanitin in concentrations of 0.005-1 µg/culture had a significant decrease in the number of transformed foci. This reduction in transformed focus formation was thought to be caused by a general impairment of cell growth when the  $\alpha$ -amanitin concentration was greater than 0.01 µg/culture.

- 2526 COMPLEMENT-FIXATION ANTIBODIES TO ADENOVIRUS-ASSOCIATED VIRUSES, ADENOVIRUSES, CYTOMEGALOVIRUSES AND HERPES SIMPLEX VIRUSES IN PATIENTS WITH TUMORS AND IN CONTROL INDIVIDUALS. (E.) Sprecher-Goldberger, S. (Pasteur Inst., Brussels, Belgium),



L. Thiry, N. Lefebvre, D. Dekegel and F. de Halleux.  
*Amer J Epidemiol* 94(4):351-358, 1971.

A study of 292 adults and 45 children with tumors from hospitals of the University of Brussels and the University of Louvain and an equal number of control individuals was conducted to determine the complement-fixation (CF) antibodies to adenovirus-associated viruses (AAV), adenoviruses, cytomegaloviruses (CMV) and herpes simplex viruses (HSV). The cancer patients studied had: 1) a low prevalence (15.5% vs 34% for the controls) of CF antibodies to AAV type 3 which could not be attributed to an immunodepressive state; (the prevalence of AAV type 1 and 2 antibodies was nearly the same in both groups); 2) adenovirus antibodies which were significantly more frequent in sera with AAV type 2 antibodies (54% vs. 29% for sera without AAV type 2 antibodies); and 3) CMV antibodies which were associated with AAV type 3 antibodies (55% in the sera with AAV type 3 antibodies vs. 33% of the sera without these antibodies). There was no significant association between CF antibodies to HSV and AAV antibodies. Cervical carcinoma cases had a significantly higher prevalence of adenovirus antibodies in sera with AAV type 3 antibodies than the controls. In other cervical cancer cases a high prevalence of HSV type 2 without AAV infections was found.

2527 TEMPERATURE-SENSITIVE MUTANTS OF ADENOVIRUS DEFECTIVE IN INTERFERON INDUCTION AT NON-PERMISSIVE TEMPERATURE. (E.) Ustacelebi, S. (Virol. Unit., Glasgow, Scotland) and J. F. Williams. *Nature* 235(5332):52-53, 1972.

Ten temperature-sensitive (*ts*) mutants of adenovirus type 5 have been tested for ability to induce interferon in chick embryo fibroblast (CEF) cells at the permissive (31°C) and non-permissive (38°C) temperatures. Primary CEF cells seeded two to three days previously were infected with wild type or mutant virus. After two hr absorption at 38°C half the cells were incubated for three days at 38°C and the other half for four days at 31°C. Good yields of interferon in CEF cells were induced at 31°C by all mutants and the wild type virus. The wild type virus and all *ts* mutants induced normal yields of interferon at 38°C; however, *ts*18 and *ts*19 failed to induce interferon at 38°C. Double infection of CEF cells with *ts*18 and *ts*19 was performed to determine whether these mutants also complemented each other with respect to interferon induction; negative results were obtained. Further studies are being carried out to investigate this failure to complement.

2528 MITOCHONDRIAL DNA FROM HAMSTER TUMORS INDUCED BY ADENOVIRUS TYPE 12. (E.) Nishida, S. (Okayama U. Med. Sch., Japan) and T. Oda. *Acta Med Okayama* 24(6):551-557, 1970.

Electron microscopy was used to observe mitochondrial

DNA from hamster tumors induced by adenovirus type 12 (Ad 12). Syrian hamsters were injected i.p. with Ad 12 within 24 hr after birth; tumors were excised, minced and homogenized 48 days later and the cell suspension was injected s.c. into 45- to 60-day-old unconditioned hamsters. The animals were sacrificed two weeks later, the tumors excised, and mitochondrial DNA isolated. Many small linear DNA fragments, usually less than 2  $\mu$  in length, and many circular DNA fibers were seen by electron microscopy. The mean value of the length of the highest frequency group of circular mitochondrial DNA molecules was  $4.92 \pm 0.38 \mu$ . It is suggested that the short linear DNA fibers observed resulted from the breaking of some mitochondrial DNA molecules when the DNA was extracted.

2529 MULTIPLICITY REACTIVATION OF HUMAN ADENOVIRUS TYPE 12 AND SIMIAN VIRUS 40 IRRADIATED BY ULTRAVIOLET LIGHT. (E.) Yamamoto, H. (Natl. Inst. Hlth., Tokyo, Japan) and H. Shimojo. *Virology* 45(2):529-531, 1971.

Multiplicity reactivation (MR) of purified UV-irradiated and unirradiated adenovirus type 12 (Ad-12) and SV40 (strain ConII) was evaluated in terms of plaque and infectious center formation. When assayed by plaque formation, lower dilutions ( $10^{-0.5}$  to  $10^{-2}$ ) of UV-irradiated virus produced from two to 12 times more plaques than expected, indicating that MR may have occurred. Similar results were obtained when infectivity was assayed by infectious center formation. Lower dilutions of UV-irradiated Ad 12 or SV40 produced more infectious centers than those expected by the multiplicity of infection and the plating efficiency of infectious centers with unirradiated virus and it was calculated that approximately 320 virions of Ad-12 or 100 virions of SV40 per cell might be enough to induce MR.

2530 NONPRODUCTIVE INFECTION AND INDUCTION OF CELLULAR DEOXYRIBONUCLEIC ACID SYNTHESIS BY BOVINE ADENOVIRUS TYPE 3 IN A CONTACT-INHIBITED MOUSE CELL LINE. (E.) Tsukamoto, K. (Inst. Virus Res., Kyoto U., Japan) and Y. Sugino. *J Virol* 9(3):465-473, 1972.

DNA synthesis in contact-inhibited mouse kidney cells (C3H2K) infected with bovine adenovirus type 3 (BAV-3) was studied by autoradiography and scintillation spectrometry after a pulse label with  $^3\text{H}$ -thymidine. When BAV-3 infection took place in medium either with or without serum, DNA synthesis was stimulated to a greater extent than in control cells stimulated with serum-containing medium. Although virus-infected C3H2K cells showed morphological changes resembling a cytopathic effect, no BAV-3 multiplication was detected. The morphological change seen in infected cells was transmitted to some progeny cells. Fluorescence antibody tests revealed the presence of T antigen in nuclei of nearly all infected cells. Hybridization studies

indicated that DNA synthesis induced by virus infection in contact-inhibited C3H2K cells was entirely cellular with no detectable synthesis of viral DNA. Titration experiments showed that the extent of induction of cellular DNA synthesis in virus-infected cultures was closely correlated with the multiplicity of infection. DNA synthesis began to rise from 0.1 TCID<sub>50</sub> per cell and reached a plateau at about 1.0 TCID<sub>50</sub> per cell. Virus infection of the medium-stimulated cells did not prevent entry into mitosis.

- 2531 VIRUS-CODED ORIGIN OF A LOW MOLECULAR WEIGHT RNA FROM KB CELLS INFECTED WITH ADENOVIRUS 2.  
(E.) Ohe, K. (Dept. Bacteriology, U. Alberta, Edmonton, Canada). *Virology* 47:726-733, 1972.

Cultured human epithelioid KB cells infected with adenovirus 2 (Ad2) had previously been shown to synthesize a unique species of low-molecular weight RNA (VA RNA), which annealed with both KB and Ad2 DNA. In these experiments, <sup>32</sup>P-labeled VA RNA was purified by ultracentrifugation, deoxyribonuclease I treatment and polyacrylamide gel electrophoresis, and was hybridized in the presence of 40% formamide with <sup>3</sup>H-labeled DNA purified from Ad2, KB cells or *E. coli* by ribonuclease treatment and phenol-SDS extraction. Incubation of Ad2 DNA with saturating amounts of VA RNA showed that 3.19 X 10<sup>-3</sup> µg of VA RNA was hybridized per 2 µg of Ad2 DNA; this corresponded to 0.74 copy of VA RNA. Binding of VA RNA to KB DNA was only 14% of that of VA RNA to Ad2 DNA. When a fixed quantity of VA RNA was hybridized with increasing amounts of Ad2 or KB DNA, a maximum of 66% annealed to Ad2 DNA, but no significant amount hybridized with KB DNA. No increase in the amount of VA RNA hybridized to excess Ad2 DNA was observed when ribonuclease treatment of the hybrids was omitted. These results indicate that the entire molecule of VA RNA was hybridized with Ad2 DNA and it is concluded that VA RNA is coded by the infecting viral genome.

- 2532 INDUCTION OF LIVER TUMORS IN MICE WITH MONKEY ADENOVIRUS SA7(C8). (Rus.)  
Irlin, I. S. (N.F. Gamaleya Inst. Epidemiol. Microbiol., Acad. Med. Sci. USSR, Moscow), V. S. Ter-Grigoriev, A. D. Al'tshtein, N. N. Dodonova, T. I. Biryulina and N. I. Kuprina. *Vop Onkol* 17(9): 76-80, 1971.

After a latent period of two wk to 1.5 months, single or multiple liver tumors were found in 10/12 and 5/6 newborn C3H/He mice injected s.c. with small- and large-plaque variants of monkey adenovirus SA7 (C8), resp. Liver tumors were also found in 2/6 newborn mice injected intracerebrally with the large-plaque variant of this virus. Neither variant had any carcinogenic effect in adult mice. Both variants also induced liver tumors in newborn C3HA, CC57W, and BALB/cDe mice, but with much lower frequencies than in C3H/He mice. Extrahepatic metastases were found in the mesentery and circumportal lymph nodes

in 3/43 mice; in 1/3 the liver appeared intact on gross examination. Histological examination of the tumors revealed two types of cells with sarcomatous and carcinomatous features, resp. The histological findings and the failure to find any organ-specific liver antigen in the tumors suggest that these tumors originate in connective tissue. Passage of cells from these tumors into adult isologous mice induced tumors only at the site of injection after 4-6 wk; no metastases were observed. In about 50% of cases, serum from mice with primary or transplanted liver tumors gave a positive complement fixation reaction with antigen from mouse liver tumors or s.c. hamster tumors induced with monkey SA7(C8) adenovirus.

- 2533 EXPERIMENTAL INFECTION OF HUMAN CERVIX BY HERPESVIRUS TYPE 2 IN ORGAN CULTURE.  
(E.) Balduzzi, P. C. (U. Rochester Sch. Med. Dent., N.Y.), M. A. Nasello and M. S. Amstey. *Cancer Res* 32(2):243-246, 1972.

The progressive development of herpesvirus type 2 infection in human cervical tissues, maintained in organ culture, is studied. Strips of endocervical and ectocervical epithelium with some underlying stroma, from specimens obtained after hysterectomy for benign disease, were established in organ culture and infected with a herpesvirus type 2 (Lewis strain). Controls consisted of fragments of cervical epithelium incubated in medium without the virus. After a 2-hr incubation at 37°C, four or five fragments were placed in glass screw cap vials containing F-12 medium; vials were incubated at 37°C in 5% CO<sub>2</sub> atmosphere. At various intervals fragments were removed, processed, stained with hematoxylin and eosin and examined by light microscopy, at low and high magnifications. Excellent histological details of glands, surface epithelium, stromal elements and vascular endothelium were seen in both control and infected tissues for 23 days (the longest time any culture was held). In the cultures exposed to herpesvirus type 2, evidence of infection in both the stromal and epithelial cells at the surface of the endocervical fragments was seen as early as 48 hr postinfection; and in 72 hr the typical intranuclear inclusions had progressed to the ectocervical area. At 5-6 days cells with ground-glass nuclei and chromatin margination or vacuolated nuclei appeared predominately in the stroma and squamous epithelium of the ectocervix, with the basal or parabasal cell layers showing these changes, and with the superficial layers appearing normal in the squamous epithelium of the cervix. Extensive involvement of the stromal elements of the endocervical cultures occurred after six days, after eight days all cellular types were affected by herpesvirus infection with rapid progression of the infection through the following week. No evidence was found for cytological atypia, other than obvious herpetic changes, up to 19 days postinfection; however, this does not rule out the possibility that these changes could be induced in the tissues with more prolonged organ cultures under optimum conditions.



2534 DIFFERENCES IN THYMIDINE KINASE-INDUCING ABILITY OF HERPESVIRUS TYPES 1 AND 2.

(E.) Lowry, S. P. (Baylor Coll. Med., Houston, Texas), E. Bresnick and W. E. Rawls. *Virology* 46(3): 958-961, 1971.

Herpesvirus types 1 and 2 were found to differ in their ability to induce TdR kinase in rabbit kidney cells; this difference was observed when both high and low multiplicities of virus were used to infect the cells. The high levels of TdR kinase induced by the type 1 virus correlated well with its sensitivity to 5-iodo-2'-deoxyuridine (IUdR), while the low levels of TdR kinase induced after type 2 infection corresponded to its relative resistance to this inhibitor. The enzymes induced in rabbit kidney cells were tested for their optimum pH. The activity of both type 1- and type 2-induced enzymes was reduced at pH 5; however, the optimum activity of the type 1-induced enzyme was found to be at pH 6, while the type 2 enzyme had optimum activity at pH 7. It is believed that both type 1- and type 2-induced enzymes are at least partially controlled by the host cell, in that the levels of enzyme were influenced by the host in which the enzyme was induced.

2535 ANTIBODIES TO SURFACE ANTIGENS OF HERPESVIRUS TYPE 1- AND TYPE 2-INFECTED CELLS AMONG WOMEN WITH CERVICAL CANCER AND CONTROL WOMEN. (E.) Smith, J. W. (Baylor Coll. Med., Houston, Texas), S. P. Lowry, J. L. Melnick and W. E. Rawls. *Infect Immun* 5(3):305-310, 1972.

Monolayers of chick embryo cells (CE) were infected with herpesvirus types 1 or 2 and sera from virus-infected women, or from women with cervical cancer, were added to the infected cells. Indirect immunofluorescence was used to study test sera for antibodies to surface antigens of herpesvirus. Antibodies to virus surface antigens could be detected by surface immunofluorescence in infected CE cells using sera from patients with herpesvirus type 1 and type 2. The surface immunofluorescence reaction was specific; uninfected cells and cells infected with viruses other than herpes failed to react when incubated with sera containing antibodies to herpesvirus. When reference sera were increasingly diluted, the intensity of the fluorescence antigen reaction declined. Antibody titers to surface antigens in herpesvirus type 1-infected CE cells incubated with sera from virus-infected patients correlated well with the titers of neutralizing antibodies to herpesvirus type 1. A similar correlation of surface antigen antibodies and neutralizing antibodies was seen when CE cells infected with herpesvirus type 2 were incubated with sera from patients with herpesvirus type 2 infections, and when infected CE cells were incubated with sera from 30 cervical cancer patients or with sera from 30 matched healthy controls. Cancer patients did not show unusually high or low titers of antibody activity to surface antigens.

2536 INDUCTION OF LYMPHOID HYPERPLASIA AND LYMPHOMA-LIKE DISEASE IN RABBITS BY HER-

*PESVIRUS SYLVILAGUS*. (E.) Hinze, H. C. (Dept. Med. Microbiol., U. Wisconsin, Madison). *Int J Cancer* 8:514-522, 1971.

Sixty wild cottontail rabbits (30 young and 30 adult) were inoculated i.p. or s.c. with  $10^5$  plaque-forming U of *Herpesvirus sylvilagus*, a virus isolated from naturally infected cottontails. Animals were observed for 18 wk postinoculation. All inoculated animals showed virus present in blood 1-2 wk post-inoculation; virus was present in small amounts in the blood for the duration of the observation period. Consistent lymphocytosis was seen in inoculated rabbits beginning 2-3 wk postinoculation. Large, immature and abnormal lymphoid cells appeared in peripheral blood two wk postinfection. General lymphadenopathy began in adult and young rabbits at two wk and increased over the next 4-6 wk. Spleen and lymph node hyperplasia were seen 2-3 wk postinoculation; in some cases, hyperplasia approached a condition resembling malignant lymphoma. More young rabbits than adults (27% vs 10%) showed malignant lymphoma-like development. Most infected animals showed infiltration of organs with immature lymphoid cells.

2537 OCULAR PATHOGENICITY OF TYPES 1 AND 2 *HERPESVIRUS HOMINIS* IN RABBITS. (E.) Oh, J. O. (Proctor Fdn., U. California, San Francisco), G. B. Moschini, M. Okumoto and T. Stevens. *Infect Immun* 5(3):412-413, 1972.

Clinical manifestations of *Herpesvirus hominis* (HVH) types 1 and 2 infections of the rabbit eye are compared. Both eyes of five or six New Zealand White male rabbits were used to test each strain; seven strains of each type of HVH were used. Approximately  $10^5$  50% tissue culture infectious doses of HVH were instilled to either intact or abraded corneas. The main lesions produced were conjunctivitis, corneal ulceration, pannus and iritis. Effects of all seven type-1 HVH strains began to appear on day 3 or 4 postinfection, regressing rapidly after day 7; type-2 HVH-infected eyes did not show effects until much later, from day 5 to day 12. The type 2 lesions were, however, more severe and of longer duration. Abraded corneas infected with type 1 or 2 HVH showed onset of conjunctivitis two or five days earlier, resp., than did the intact corneas.

2538 ANTIBODY TO *HERPESVIRUS HOMINIS* TYPES 1 AND 2 IN PATIENTS WITH HODGKIN'S DISEASE AND CARCINOMA OF THE NASOPHARYNX. (E.) Catalano, L. W., Jr. (Natl. Inst. Neurol. Dis. Stroke, Bethesda, Md.) and J. M. Goldman. *Cancer* 29(3): 597-602, 1971.

Sixty patients, 40 with Hodgkins' disease and 20 with nasopharyngeal carcinoma (NPC), were studied for neutralizing antibodies to both strains (types 1 and 2) of *Herpesvirus hominis* (HVH) by the micro-neutralization test. Control sera, obtained from blood donors and orthopedic patients (teenagers),

were matched, as closely as possible for age, sex and race. Male patients with Hodgkins' disease showed a greater incidence of type 2 HVH antibody than the controls. This difference could not be accounted for on the basis of histologic type of Hodgkin's disease. Patients with a mixed cellular histologic type had a greater incidence of type 2 HVH antibody. Statistical analysis of the geometric mean titers (GMT) of the patient sera for both types 1 and 2 herpesviruses revealed no significant differences from control sera mean titers. No increased incidence of either type of HVH antibody was detected in patients with NPC, as a group, but individuals with NPC had higher serum titers to the type 2 strain of HVH than the donor controls but no titer differences were noted when patients with NPC were compared to patients with head and neck tumors. The data do not support a relationship of HVH to NPC but do indicate that additional information is needed for clarification of the role of HVH in patients with Hodgkins disease.

2539 IMPAIRMENT OF HERPESVIRUS GROWTH IN CHICK EMBRYO FIBROBLAST CULTURES BY  $\alpha$ -AMANITIN.

(E.) Mannini-Palenzola, A. (Inst. Microbiol., U. Bologna, Italy), F. Costanzo, and M. La Placa. *Archiv Ges Virusforsch* 34(4):381-384, 1971.

The effect of  $\alpha$ -amanitin on the growth of vaccinia virus (VV), frog virus type 3 (FV 3) and herpes virus (HV) was studied to determine if  $\alpha$ -amanitin could be used to discriminate between viruses which utilize cellular DNA-dependent RNA polymerases and viruses which do not need it. KB cells and secondary chick embryo fibroblasts (CEF) were placed in serum-free medium with or without 3  $\mu$ g/ml  $\alpha$ -amanitin 1 hour before virus infection. The viral yield of VV and HV was not altered significantly by  $\alpha$ -amanitin in KB cells; the growth of VV and FV 3 were not influenced by the presence of  $\alpha$ -amanitin in CEF. However, the growth and cytopathic effect of HV on CEF was selectively impaired by  $\alpha$ -amanitin. In KB cell cultures  $\alpha$ -amanitin slightly depressed RNA synthesis and RNA polymerase II activity after 20 hr of contact, while in CEF cultures both RNA synthesis and polymerase II activity were noticeably impaired after six hr of exposure. It is suggested that a cellular DNA-dependent RNA polymerase is necessary at some stage of HV growth.

2540 ANTIBODIES TO HERPES-TYPE VIRUS IN NASOPHARYNGEAL CARCINOMA AND CONTROL GROUPS. (E.)

Lin, T. M. (Natl. Taiwan U. Coll. Med., Taipei), C. S. Yang, S. W. Ho, J. F. Chiou, C. H. Liu, S. M. Tu, K. P. Chen, Y. H. Ito, A. Kawamura and T. Hirayama. *Cancer* 29(3):603-609, 1972.

Sera collected from 117 patients with nasopharyngeal carcinoma (NPC), in Taiwan, were titrated for antibodies to herpes-type virus (HTV) in a Burkitt's lymphoma cell line (P3HR-1) by the immunofluorescence antibody technique (FA). The results were compared

with 306 neighborhood controls matched by age and sex, with 303 patient families and with 538 neighborhood control families. Antibody titers were higher in the NPC cases than in any of the three control groups. Dissociations in the frequency distributions of antibody titers in the NPC and healthy control groups were found to be maximum when the limiting value was set at 1:640. No significant differences were observed in the percentage distribution of anti-HTV titers in the three control groups. The percentage of "sero-positive" cases was 40% for NPC patients and 5, 5, and 6% resp. for the control groups. The geometric mean titer for NPC patients was 1:242, while only 1:65, 1:69 and 1:61 was recorded in the control groups. Statistical analysis on the distribution exhibit significantly higher ridit scales than control groups. Data indicated close association of NPC risk with antibody titers, persons with titers of 1:640 and 1:2560 having more than 30 times and 200 times, resp. the NPC risk of those with antibody titers of less than 1:40. No indication of household aggregation of "sero-positive" cases was found in either the patient family control group or in the neighborhood control families. This may suggest that infection by HTV is sporadic in nature. Further study is recommended to clarify this point.

2541 STUDIES ON ARGINYL TRANSFER RIBONUCLEIC ACID IN HERPES VIRUS INFECTED BABY HAMSTER KIDNEY CELLS. (E.) Bell, D. (Inst. Virol., U. Glasgow, Scotland), N. M. Wilkie and J. H. Subak-Sharpe. *J Gen Virol* 13(3):463-475, 1971.

The presence of a proposed herpes virus-specific arginyl tRNA in infected cells was investigated. Purification of phage T<sub>1</sub> digests of tRNA from herpes simplex virus (HSV)-infected BHK cells by DEAE cellulose chromatography revealed two minor contaminating peaks which were due to labelling from minor contaminants of the radioactive arginine used to aminoacylate the tRNA. The two oligonucleotide contaminants were eluted just before the main peak of host material at slightly lower salt concentrations. All contaminants were eliminated by re-isolating the tRNA on DEAE cellulose after aminoacylation. The aminoacyl-tRNA bond was stabilized by N-acetylation to prevent discharging during RNase digestion. Labeled arginine charged 6.2 to 6.7% of uninfected BHK tRNA and 5.5 to 5.8% of HSV-infected BHK cells. The degree of hybridization of purified N-acetyl[<sup>14</sup>C]-arginyl tRNA from either uninfected or HSV-infected BHK cells to herpes DNA, phage T4 DNA or to non-DNA-containing control membranes was the same. Evidence for HSV-specified arginyl tRNA was not obtained in this study.

2542 SOME PROPERTIES OF THE DNA FROM A NEW EQUINE HERPESVIRUS. (E.) Ludwig, H. (Baylor Coll. Med., Houston, Tex.), N. Biswal, J. T. Bryans and R. M. McCombs. *Virology* 45(2):534-537, 1971.



The physical properties of a newly isolated equine herpesvirus, the equine coital exanthema (ECE) virus, were studied and its DNA was characterized. Electron microscopic examination of purified ECE virions showed typical herpesvirus particles with icosahedral capsids. The virus core was approximately 98 nm in diameter and enveloped particles had a diameter of approximately 198 nm. The buoyant density of purified DNA from two ECE strains was 1.725 g/cm<sup>3</sup>, corresponding to a G+C content of 66%. ECE viral DNA was double-stranded, as heat denaturation changed its buoyant density to 1.740 g/cm<sup>3</sup>. The buoyant density of ECE DNA was the same as that of herpes simplex virus type 1, but differed from that of herpes simplex virus type 2, infectious bovine rhinotracheitis virus and equine rhinopneumonitis virus. RNA-DNA hybridization experiments indicated that there was no homology between ECE virus and herpes simplex type 1 or type 2.

- 2543 DIFFERENTIAL SUSCEPTIBILITY TO HERPES SIMPLEX VIRUSES OF HAMSTER CELL LINES ESTABLISHED AFTER EXPOSURE TO CHEMICALLY INACTIVATED HERPESVIRUS. (E.) Docherty, J. J. (Milton S. Hershey Med. Ctr. Pennsylvania St. U., Hershey), F. J. O'Neill and F. Rapp. *J Gen Virol* 13(3):377-384, 1971.

The replication of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) was studied in two hamster cell lines, HDC-17, fibro-epithelial-like and partially contact-inhibited, and HDC-22, epithelial-like and not contact-inhibited. The cell lines were cloned from primary hamster cell cultures infected with the 316-D strain of HSV-2 inactivated with 7,12-dimethylbenz(a)anthracene. Chromosome analysis showed that HDC-22 was hypodiploid, and lacked a D-group chromosome, whereas HDC-17 remained diploid. HDC-17, because of its normal karyotype, was considered the control in growth studies of the replication of HSV-1 and HSV-2. No difference was found in the ability of HSV-1 to replicate in either cell line over a 96-hr period. HSV-2 replicated normally in HDC-17 but poorly in HDC-22. Results were the same for the four different HSV-1 and HSV-2 strains tested.

- 2544 STRUCTURE AND DEVELOPMENT OF VIRUSES AS OBSERVED IN THE ELECTRON MICROSCOPE: XI. ENTRY AND UNCOATING OF HERPES SIMPLEX VIRUS. (E.) Miyamoto, K. (Coll. Phys. Surg., Columbia U., New York, N.Y.) and C. Morgan. *J Virol* 8(6):910-918, 1971.

The sequential events following entry of the capsid of the Miyama strain of herpes simplex virus (HSV) into monolayer cultures of HeLa cells were studied by electron microscopy. After exposure to HSV, two morphologically distinct types of capsids were observed on the cell surface. "Light capsids," which constituted 53% of the total capsids seen on the cell surface after 1 hr at 4°C, were characterized by a translucent zone separating the capsid from the dense core. "Dense capsids," (47% of the total) were characterized by a fine granularity in the

translucent zone. Both types were seen to fuse with the cell membrane. Only dense capsids disintegrated in the cytoplasm, presumably releasing their core soon after entry into the cell. The light capsid was more stable and was frequently seen close to the nucleus. Of the HSV particles 4-7% lacked cores but were still able to enter the cytoplasm. By 20-30 min postinfection, light capsids had passed to the perinuclear region and had lost their cores. By two hr postinfection 90% of intracytoplasmic capsids were empty, the entry process having been completed by one hr postinfection. Pretreatment of the cells with puromycin or actinomycin D (act D) had no effect on HSV entry but markedly reduced the number of intracellular capsids releasing their cores and slowed capsid dissolution. Treatment with act D after infection had no effect. UV-irradiation of virus for 5 min did not prevent HSV entry but inhibited release of core material. UV-irradiation for 30 min, however, destroyed all infectivity. It is suggested that both types of particles may be necessary to initiate HSV infection, and that the DNA released by the dense capsid shortly after entry is transcribed into a virus-specific RNA, which codes for an enzyme capable of altering the permeability of the light capsid from which the infectious DNA then escapes.

- 2545 CELL-TO-CELL TRANSMISSION OF HERPES SIMPLEX VIRUS IN PRIMARY HUMAN AMNION CELLS. (E.) Christian, R. T. (U. Michigan, Ann Arbor,) and P. Ludovici. *Proc Soc Exp Biol Med* 138(3):1109-1115, 1971.

Herpes simplex virus (HSV)-induced DNA synthesis within the different bands of a microepidemic was studied by radioautography, time-lapse photography and the fluorescent antibody technique. The HSV strain used was acquired from primary human isolates and the cells were prepared from primary human amnion. Stationary-phase cells (5-10 days after trypsinization) were infected with 10-100 plaque-forming units of HSV. Cultures were labeled in maintenance medium by exposure to 0.1 Ci/ml of tritiated thymidine (Tdr<sup>3</sup>H) for one hr. Normal cells were irradiated with a single continuous dose of x-ray at 5000 R prior to the introduction of the viral agent so that virus-induced DNA synthesis could be distinguished from normal cellular DNA synthesis. Time-lapse photography showed three important characteristics of plaque formation: 1) the plaque is formed by the retraction of cell sheets; 2) only cells in direct contact with infected cells become virus-infected and 3) the sequence of infection is preserved as the cell sheet retracts. The microepidemic appeared to develop largely by transmission of the virus through intercellular bridges, as both Tdr<sup>3</sup>H-labeled DNA and specific HSV protein were found in these areas.

- 2546 DETECTION OF VIRUS-ASSOCIATED ANTIGEN ON MEMBRANES OF CELLS PRODUCTIVELY INFECTED WITH MAREK'S DISEASE HERPESVIRUS. (E.) Ahmed, M.

(Pfizer, Inc., Maywood, N.J.) and G. Schidlovsky. *Cancer Res* 32(2):187-192, 1972.

A cell membrane antigen synthesized as a result of Marek's disease herpesvirus (MDHV) infection has been found at the outer surface of viable cells, using Marek's disease (MD)-infected chicken sera with a membrane immunofluorescence (MIF) test. MD chicken sera were tested with MIF and fixed-cell immunofluorescence (FIF) tests to localize intracellular and membrane antigens of MDHV-infected chick kidney cell culture. Live cells showed only a ring-type fluorescence, indicating that reactive antigen groups were present at the cell surface. Epithelial and fibroblast-like cells adjacent to the area showing this cytopathic effect did not have the membrane antigen. The chicken sera reacting with intracellular antigens in the FIF test also reacted with the membrane antigens of MDHV-infected cells in the MIF test. When MIF-positive sera were allowed to react with live MDHV-infected cells, the formation of antigen-antibody complexes at the cell surface could be observed by electron microscopy. It is concluded that sera from MD-infected chickens do not have antibodies that react in FIF or MIF tests with lymphoid tumor cells from diseased chickens. Further studies are needed to identify tumor cell antigens in Marek's disease.

2547 GROWTH OF HERPES SIMPLEX VIRUS IN CULTURES OF DISSOCIATED HUMAN NERVOUS TISSUE. (E.)

Rajcani, J. (Hosp. Sick Children Mental Retardation Ctr., Toronto, Canada) and B. S. Scott. *Acta Virol* 16:25-30, 1972.

The growth of purified herpes simplex virus (HSV) was followed in cultures of dissociated embryonic human spinal root ganglia by means of virus titration and the fluorescent antibody (FA) technique. An increase in extracellular HSV occurred in the medium 12 hr post-infection (p.i.) and reached a maximum at 24 hr p.i. Virus multiplication occurred in both neurons and non-neuronal fibroblast-like cells. Maximum extracellular virus levels coincided with the onset of cytopathic changes, as seen by phase-contrast microscopy. The first traces of virus antigen were detected in the neurons at the nuclear margin by FA at nine hr p.i. Cytoplasmic fluorescence developed between 12-16 hr p.i. and coincided with a loss of nuclear fluorescence and an elevation in the extracellular HSV titer. In the non-neuronal cells, the virus antigen formed larger granules and clumps in the paranuclear area of cytoplasm nine hr, p.i. By 24-48 hr p.i., neurons showed nucleolar disaggregation, an empty nuclear appearance, loss of fine internal structure of the cytoplasm, and retraction of neuronal processes. Non-neuronal cells showed more extensive pathology with rounding and detachment from the collagen surface and bright cytoplasmic fluorescence. No obvious giant cell formation was seen in any infected cultures.

2548 RESCUE OF THE GENOME OF THE DEFECTIVE MURINE SARCOMA VIRUS FROM A NON-PRODUCER

HAMSTER TUMOR CELL LINE, PM-1, WITH MURINE AND FELINE LEUKEMIA VIRUSES AS HELPERS. (E.) Monti-Bragadin, C. (Inst. Microbiol., U. Padova, Italy) and K. Ulrich. *Int J Cancer* 9(2):383-392, 1972.

A cell line, PM-1 cl6 (PM-1) derived from a Harvey murine sarcoma virus (H-MuSV)-induced hamster tumor is described; the PM-1 cells were found to carry the defective MuSV genome but appeared in various tests to be free of MuSV and hamster-tropic sarcoma-inducing virus. Tissue culture fluids and cell-free extracts of PM-1 cells were tested for the presence of infectious murine leukemia virus (MuLV) on mouse embryonal fibroblast (MEF) cultures by plaque assay. In no case were plaques or syncytia formed by the PM-1 cells. Indirect immunofluorescence studies with immune serum against MuLV gs-antigens yielded negative results in PM-1 cells. PM-1 cells were labeled with <sup>3</sup>H-uridine and their supernatant fluids were analyzed for newly synthesized virus by examining the distribution of radioactivity after centrifugation on sucrose gradients. Uninfected and Rauscher MuLV-infected MEF cultures were also tested as controls. Radioactive peaks were obtained in fractions corresponding to a density of 1.16 g/cm<sup>3</sup> in gradients prepared from control cells. No similar peaks were seen with PM-1 cells, indicating that newly synthesized virions were absent from PM-1 cells. When cell-free extracts of PM-1 cells were injected s.c. into 24 hamsters, none of the animals developed tumors, indicating that PM-1 cells contained no hamster-specific virus. In an attempt to rescue the MuSV genome from PM-1 cells, focus-forming activity of cell-free extracts from mixed cultures of PM-1 cells and MuLV-infected mouse 3T3 cells was assayed on cultures of 3T3 cells. Transforming activity was seen in all cases where PM-1 cells were cultivated together with MuLV-infected cells. Five chemically-induced murine leukemias could also rescue the MuSV from PM-1 cells. Rescue of focus-forming activity from the PM-1 cell line by cocultivation with feline embryonic cells and feline leukemia virus as helper was also effected.

2549 CELL LINE DERIVED FROM A MURINE SARCOMA VIRUS (MOLONEY PSEUDOTYPE)-INDUCED TUMOR: CULTURAL, ANTIGENIC, AND VIROLOGICAL PROPERTIES. (E.) Massicot, J. G. (Nat'l. Cancer Inst., Bethesda, Md.), W. A. Woods and M. A. Chirigos. *Appl Microbiol* 22(6):1119-1122, 1971.

A cell line (MSC) derived from murine sarcoma virus (Moloney pseudotype, MSV-M)-induced tumors in adult BALB/c mice has been established. Two cell types were present in equal numbers: fibroblast-like, firmly attached cells and rounded, loosely attached ones. The fibroblast-like cells grew in a disoriented manner and were not contact-inhibited. Both cell types were positive for the gs-1 murine leukemia virus and Moloney type-specific membrane fluorescent antigens. Release of <sup>51</sup>Cr from prelabelled MSC cells could be effected by MSV-M type-specific cytotoxic antibody in the presence of guinea pig or rabbit complement but not with heated guinea pig or rabbit serum. <sup>51</sup>Cr could also be released in the presence of



spleen cells from BALB/c mice which had regressed MSV-M tumors. MSC cells released defective MSV-M and a Moloney-type leukemia virus. MSC cells maintained tumor-producing ability *in vitro* through eight months of culture.

- 2550 RAPID RESCUE OF THE DEFECTIVE M-MSV GENOME BY THE USE OF CELL FUSION. (E.) Kelloff, G. J. (Natl. Inst. Hlth., Bethesda, Md.), R. J. Huebner, C. Long and R. V. Gilden. *Virology* 46(3): 965-968, 1971.

A method for the rapid rescue of the Moloney strain of murine sarcoma virus (M-MSV) by Sendai virus-induced fusion of HT-1 cells derived from a M-MSV-induced hamster tumor with a cell line shedding a murine virus is reported. The HT-1 cells were fused with Rauscher leukemia virus-infected 3T6 cells. Experimental data indicated that defective M-MSV genomes could be rescued within two hr after fusion in the presence of Sendai virus. Further studies investigating metabolic requirements for rescue are presently being performed.

- 2551 IMMUNOFLUORESCENT DETECTION OF MURINE AND HAMSTER C-TYPE VIRUS SPECIES-SPECIFIC (gs-1) DETERMINANTS BY MONOSPECIFIC GUINEA-PIG SERA AND INTERSPECIES-SPECIFIC (gs-3) DETERMINANTS BY TUMOR BEARING RAT SERA. (E.) Hampar, B. (Natl. Cancer Inst., Bethesda, Md.), R. V. Gilden, G. Kelloff, S. Oroszlan and D. Simms. *Int J Cancer* 8:425-431, 1971.

A line of mouse cells (F-4) infected with Rauscher leukemia virus (RLV) and a line of hamster embryo cells infected with hamster leukemia virus (HaLV) were reacted with guinea pig antisera to species-specific (gs-1) antigens (antigens isolated from mouse, hamster and cat C-type viruses), or with antisera from rats immunized with homogenates of a murine sarcoma virus. Complement fixation tests with the anti-gs-1 guinea pig sera showed that both RLV- and HaLV-infected cells possess 32-64 complement fixing U of gs-1 antigen. In complement fixation and agar gel immunodiffusion tests, guinea pig antisera showed specific reactivity for mouse or hamster gs-1 determinants, but none for the interspecies-specific (gs-3) determinants. Reactivity for the gs-3 determinants, however, was shown by rat antisera. In direct immunofluorescence (FA) tests, anti-mouse gs-1 antisera stained RLV-infected cells but not HaLV-infected cells, while anti-hamster gs-1 sera stained HaLV-infected cells but not RLV-infected cells. Rat antisera also detected gs-3 determinants in HaLV-infected cells using FA. FA staining was limited to cytoplasm of infected cells. Two types of cytoplasmic staining were seen; punctuate foci associated especially with structures near the cell membrane; and diffuse staining in the perinuclear region. Experiments with the blocking of FA-staining of RLV-infected cells by anti-mouse gs-1 guinea pig sera indicated that gs-1 and gs-3 determinants reside on the same molecule, gs-1 having a more dominant accessible location than gs-3.

- 2552 AN INFECTIOUS DNA INTERMEDIATE WHICH TRANSFORMS ROUS SARCOMA VIRUS IN CHICK CELLS TRANSFORMED BY THIS VIRUS. (Fr.) Montagnier, L. (Curie Fdn., Radium Inst. Essone, France) and Ph. Vigier. *C R Acad Sci [D] (Paris)* 224(13):1977-1980, 1972.

Existing experimental evidence postulating the existence of DNA as an intermediary in the replication of the tumorigenic virus has found support in experiments in which DNA extracted from chick embryo fibroblasts transformed by the Schmidt-Ruppin strain of the Rous virus has proven to be infectious. When the extract was processed by the Marmur method and inoculated into a primary chick fibroblast culture, it gave transformed cells producing the initial virus with identical phenotypic characteristics. The infectious DNA had a molecular weight of about 6 million and appears to be closely related to chromosomal DNA. In 7 experiments with DNA extracted by the Marmur method, 2 were positive; in one case transformed cells appeared on the 22nd day, in the second case on the 14th day. The cells multiplied rapidly and produced the virus in the culture medium. DNA extracted by the Hirt method showed infectious DNA was present in the chromosome fractions. The appearance of Rous cells was always accompanied by virus production in the supernatant liquid of antigenic phenotype D of the original virus.

- 2553 RIBONUCLEIC ACID DIRECTED DEOXYRIBONUCLEIC ACID SYNTHESIS BY THE PURIFIED DEOXYRIBONUCLEIC ACID POLYMERASE OF ROUS SARCOMA VIRUS. CHARACTERIZATION OF THE ENZYMATIC PRODUCT. (E.) Taylor, J. M. (Dept. Microbiology U. California, San Francisco), A. J. Faras, H. E. Varmus, W. E. Levinson and J. M. Bishop. *Biochemistry* 11(12): 2343-2551, 1972.

DNA polymerase purified from the Schmidt-Ruppin strain of Rous sarcoma virus (RSV) was used to direct synthesis of both single- and double-stranded DNA with 70S viral RNA used as template. Secondary structure of the enzymatic product was evaluated by both fractionation on hydroxylapatite and treatment with single strand-specific *Neurospora* nuclease. Both techniques gave identical results, indicating that the early "double-stranded" DNA product included single-stranded regions. The reaction product obtained from an 18 hr reaction consisted almost entirely of intact double helices. A variable portion of the early double-stranded product could not be irreversibly heat-denatured unless first "nicked" by limited hydrolysis with DNase. The nearest-neighbor nucleotide composition of this nondenaturable DNA was not significantly different from that of unfractionated enzymatic product. Both single- and double-stranded enzymatic product contained nucleotide sequences which hybridized with the RNA template, and DNAs transcribed from two different avian tumor virus RNAs (RSV and AMV) shared extensive sequence homology. Nascent DNA was hydrogen-bonded to the high-molecular-weight template RNA and covalently linked to a low-molecular-weight polyribonucleotide. No DNA was released from template molecules without concomi-

tant degradation of the RNA. The length of DNA chains synthesized by purified polymerase was identical with that of DNA synthesized by detergent-activated virions. Both virions and purified enzyme preferentially transcribed limited and homologous regions of viral RNA into double-stranded DNA.

- 2554 COMPARATIVE CHROMOSOME ANALYSIS OF PRIMARY AND METASTATIC ROUS SARCOMAS IN RATS. (E.) Mitelman, F. (Inst. Path. Inst. Genetics, U. Lund Sweden). *Hereditas* 70:1-14, 1972.

Primary and secondary tumors are compared with regard to their chromosomal and histopathologic patterns. Sarcomas were induced by Rous chicken sarcoma virus in Wistar/Furth rats. Examination of chromosomes directly from these induced tumor tissues was completed on 16 lymph node metastases together with their primary sarcoma. Review of microscopic data indicated that 40% of all primary tumor tissues examined had a normal diploid stemline and approximately 70% had one or two hyperdiploid sidelines. In the metastatic tissue hyperdiploidy occurred in 2/3 of the stemlines and pseudodiploidy in 1/3 of the lines. According to karyotype analyses, the metastatic tumors are divided into four categories: 1) metastases with normal diploid stemlines and no sidelines; 2) metastases with normal diploid stemline and sidelines; 3) metastases with pseudodiploid stemlines; and, 4) metastases with hyperdiploid stemlines. Significant in the study was the close karyotype relation between these metastatic tissues and their primary tumors. Any difference noted between primary and metastatic tissue was attributed to accelerated chromosomal progression in the secondary tumor.

- 2555 AGGLUTINATION OF CHICK EMBRYO FIBROBLASTS TRANSFORMED BY THE SR-RSV STRAIN OF THE ROUS VIRUS AND BY A THERMOSENSITIVE MUTANT OF THIS VIRUS BY CONCAVALINE A. (Fr.) Biquard, J.-M. (Faculté des Sciences, Essonne, France.) and P. Vigier. *C R Acad Sci [D] (Paris)* 274(1):144-147, 1972.

Concanavaline A, a plant seed agglutinin (lectin), agglutinates animal cells transformed spontaneously, by an oncogenic virus, or by chemical carcinogens. Cellular surface areas containing sugars ( $\alpha$ -methyl-D-glucopyranoside, in the case of Concanavaline A) form bonds with agglutinins. Fibroblasts from normal chick embryos, fibroblasts from chick embryos infected with the SR-RSV strain of the Rous virus, fibroblasts from chick embryos infected with a thermosensitive mutant of the Rous virus (FU-19) incubated at 37°C, and the same fibroblasts incubated at 41°C, were agglutinated with Concanavaline A and results were evaluated. Agglutination was determined by the Burger and Goldberg method based on the percentage of agglutinated cells.

Normal cells were only weakly agglutinated, and only by very high concentrations of Concanavaline A. Agglutination of cells transformed by the Rous virus and its FU-19 mutant at 37°C was more marked, proceeded faster and occurred at lower lectin concentrations. Agglutination of cells infected with FU-19 at 41°C required much higher lectin concentrations; however, cells incubated at 41°C are more agglutinable than control cells. Because transformation and agglutinability are reversible it is suggested that these related characteristics stem from the same viral gene or group of viral genes.

- 2556 HYBRIDIZATION OF ROUS SARCOMA VIRUS DEOXY-RIBONUCLEIC ACID POLYMERASE PRODUCT AND RIBONUCLEIC ACIDS FROM CHICKEN AND RAT CELLS INFECTED WITH ROUS SARCOMA VIRUS. (E.) Coffin, J. M. (U. Wisconsin, Madison) and H. M. Temin. *J Virology* 9(5):766-775, 1972.

Rous sarcoma virus (RSV) strain B77-specific RNA purified from virus-producing chicken cells and from non-virus-producing RSV-infected rat cells was studied by hybridization with the endogenous DNA product of the RSV virion DNA polymerase system. By hybridization of the total DNA product with excess virion RNA, the product DNA was separated into hybridized ("minus") and nonhybridized ("plus") DNA. The "minus" DNA was complementary to at least 20% of the <sup>32</sup>P-labeled RNA from RSV which remained of high molecular weight after heat denaturation. A maximum of approximately 65% hybridization was observed between "minus" DNA and RSV RNA or RSV-infected chicken cell RNA. A maximum of about 60% hybridization occurred between "minus" DNA and RSV-infected rat cell RNA. RSV-infected chicken cells contained RSV-specific RNA equivalent to about 6000 virions per cell and RSV-infected rat cells contained RSV-specific RNA equivalent to approximately 400 virions per cell. Neither cell type contained detectable RNA complementary to virion RNA. The RSV-specific RNA in RSV-infected rat cells did not appear to be qualitatively different from that in RSV-infected chicken cells.

- 2557 CHICKEN FIBROBLAST TRANSFORMATION BY MEANS OF A DENATURED DNA FROM ROUS VIRUS-TRANSFORMED CELLS. (Fr.) Hillova, J. (Gustave-Roussy Inst., Villejuif, France), G. Goubin and M. Hill. *C R Acad Sci [D] (Paris)* 274(13):1970-1973, 1972.

A DNA extract from cells of an XC rat strain transformed by the Rous virus was subjected to alkaline denaturation, then added to a culture medium of chick embryo fibroblasts which, in turn, became Rous virus producers. The same procedure using denatured DNA from the rat thymus gave negative results. DNA was extracted from rat cells and from the rat thymus by the Marmur method, alkaline denaturation of DNA from XC cells was performed with 0.1 M NaOH (A), and with 0.4 M KOH (B). Cell transformation and virus production obtained by the treatment of XC



cells with denatured DNA was followed in two experimental series, each using a different stock of DNA. All cultures treated with DNA from XC cells denatured by method (A) were transformed, while cultures treated with denatured DNA from the rat thymus, DNA from XC cells denatured by method (B) and the same DNA digested with DNase were not transformed during a three-month observation period; no virus particles were found with the electron microscope. The transformed culture medium was filtered, and the presence of the virus in the filtrate was confirmed by the appearance of microtumors on chorioallantoic membranes and by the formation of conglomerates of transformed cells in secondary cultures of chick embryo fibroblasts. These results indicate that the molecular weight of infectious DNA is greater than  $0.75 \times 10^6$  and to confirm that the survival of the virus is due to DNA alone. From a concurrent determination of molecular weights of the DNA from XC cells and from the rat thymus it would also seem that the molecular weight of infectious DNA must exceed  $0.75 \times 10^6$ .

- 2558 FLUORESCENT MARKER CHROMOSOMES IN MALIGNANT LYMPHOMAS. (E.) Fleischmann, T. (U. Lund, Sweden), C. H. Hakansson and A. Levan. *Hereditas* 69(2):311-314, 1971.

Tumorous lymph nodes from seven patients with malignant lymphomas were cultured and studied cytogenetically by the fluorescence technique, with atebirin used as the stain. Cells from four of these patients contained marker chromosomes and three of these cases are reported. Although the karyotypes of these tumors were not uniform, the marker chromosomes exhibited a marked consistency. In a total of 45 cells analyzed, every cell contained one or more marker chromosomes, and among them there was consistently one or more medium-sized markers with strictly median centromere and with even fluorescence distributed equally in the two arms. The existence in all three tumors of these metacentric markers suggests that this group of lymphomas may be characterized by a specific marker.

- 2559 COMPARATIVE STUDIES OF THE CARBOHYDRATE-CONTAINING COMPONENTS OF 3T3 AND SIMIAN VIRUS 40 TRANSFORMED 3T3 MOUSE FIBROBLASTS. (E.) Sakiyama, H. (Massachusetts Inst. Technology, Cambridge) and B. W. Burge. *Biochem* 11(8):1366-1377, 1972.

Glycoproteins and glycopeptides of normal and SV-40 transformed 3T3 (SV-3T3) mouse fibroblasts were labelled with  $^3\text{H}$ -glucosamine and  $^3\text{H}$ -amino acids and analyzed. Although normal cells extracted twice as much glucosamine into the medium as did SV-3T3 cells, the glycoproteins and glycopeptides of a bulk membrane fraction of the two lines could not be distinguished by comparison of profiles of glycoproteins on acrylamide gel electrophoresis or by profiles of glycopeptides on Bio-Gel P-10 columns. No significant difference in the relative labeled sialic acid content was seen between normal and transformed cells. An observed shift toward higher

molecular weight of transformed cell glycopeptides as compared to normal 3T3 glycopeptides was probably not a consequence of transformation, since a similar shift was seen when dividing and non-dividing "normal" 3T3 cells were compared. Although there was a diversity in membrane glycopeptide sizes in both normal and transformed cells, systemic changes in these units were not a feature of virus transformation.

- 2560 TRANSCRIPTION OF THE POLYOMA VIRUS GENOME: SYNTHESIS AND CLEAVAGE OF GIANT LATE POLYOMA-SPECIFIC RNA. (E.) Acheson, N. H. (Dept. Molec. Biol., U. Geneva, Switzerland), E. Buetti, K. Scherrer and R. Weil. *Proc Nat Acad Sci USA* 68(9):2231-2235, 1971.

An experiment to define the size of late virus-specific RNA found in polyoma-infected primary mouse kidney cell cultures is reported. The size of synthesized virus-specific RNA was estimated by electrophoresis and sedimentation analysis of RNA extracts from whole cells. Newly synthesized "late" polyoma-specific RNA consists of large, heterogeneous molecules, the bulk of which ("giant RNA") have molecular weights greater than  $1.5 \times 10^6$ , the size expected for a single transcript of the polyoma genome. Treatment with dimethylsulfoxide or urea has shown that this giant RNA is not an aggregate of smaller RNA molecules. Giant polyoma-specific RNA shows a striking similarity in size distribution to nuclear messenger-like RNA (heterogenous nuclear RNA) of the host cell. Subsequent to its synthesis, some of the giant polyoma-specific RNA appears to be cleaved to at least three smaller species.

- 2561 DETECTION OF AVIAN AND MAMMALIAN ONCOGENIC RNA VIRUSES (ONCORNAVIRUSES) BY IMMUNO-FLUORESCENCE. (E.) Hilgers, J. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.), R. C. Nowinski, G. Geering and W. Hardy. *Cancer Res* 32(1):98-106, 1972.

- 2562 COMPOSITION AND SIZE OF SHOPE FIBROMA VIRUS DEOXYRIBONUCLEIC ACID. (E.) Jacquemont, B. (Natl. Inst. Hlth. Med. Res., Lyon, France), J. Grange, L. Gazzolo and M. H. Richard. *J Virology* 9(5):836-841, 1972.

- 2563 THE IDENTIFICATION OF THE 3'-HYDROXYL NUCLEOSIDE TERMINUS OF AVIAN MYELOBLASTOSIS VIRUS RNA. (E.) Erikson, R. L. (U. Colorado Med. Sch., Denver), E. Erikson and T. A. Walker. *Virology* 45(2):527-528, 1971.

- 2564 SEROLOGICAL STUDIES ON HERPES SIMPLEX VIRUSES BY NEUTRALIZATION KINETIC TEST. (E.) Kabuta, H. (Kurume U. Sch. Med., Japan), S.

Yamamoto and Y. Nakagawa. *Kurume Med J* 18(4):223-229, 1971.

2565 PREPARATION OF RNA-DIRECTED DNA POLYMERASE FROM SPLEENS OF BALB/c MICE INFECTED WITH RAUSCHER LEUKEMIA VIRUS. (E.) Yang, W.-K. (Oak Ridge Natl. Lab., Tenn.), C.-k. Koh and L. C. Waters. *Biochem Biophys Res Comm* 47(2):505-511, 1972.

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2568 VIRUS-LIKE PARTICLES IN A CASE OF VASCULITIS WITH BRAIN TUMOR. (E.) Norris, F. H., Jr. (Sch. Med. Sci., U. Pacific, San Francisco, Calif.), M. J. Aguilar and C. E. Harman. *Arch Neurol* 26(3):212-217, 1972.

2569 MURINE LEUKEMIA VIRUS ASSAY TECHNIQUES: A COMPARATIVE STUDY. (E.) Grundner, G. (Karolinska Inst., Stockholm, Sweden), E. M. Freny, V. Strouk and E. Klein. *Proc Soc Exp Biol Med* 140(1):378-387, 1972.

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2571 DEVELOPMENT OF HERPES SIMPLEX VIRUS IN THE ISOLATED NUCLEI OF Hep-2 CELLS: II. INTRANUCLEAR EVENTS IN ISOLATED HSV-INFECTED NUCLEI. (E.) Fine, D. L. (Dept. Microbiol., Pennsylvania St. U., University Park) and E. H. Ludwig. *Canad J Microbiol* 18(3):339-345, 1972.

2572 DEVELOPMENT OF HERPES SIMPLEX VIRUS IN THE ISOLATED NUCLEI OF Hep-2 CELLS: I. VIABILITY OF ISOLATED HSV-INFECTED NUCLEI. (E.) Fine, D. L. (Dept. Microbiol., Pennsylvania St. U., University Park) and E. H. Ludwig. *Canad J Microbiol* 18(3):333-337, 1972.

2573 MICROSCOPIC DETECTION OF ADVENTITIOUS VIRUSES IN CELL CULTURES. (E.) Anderson,

N. (Dept. Microbiol., U. Toronto, Ontario) and F. W. Doane. *Canad J Microbiol* 18(3):299-304, 1972.

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- 2583 EFFECT OF TRYPSIN TREATMENT OF MOUSE FIBROBLASTS AND THEIR SV40-TRANSFORMED CELLS ON THE AGGLUTININABILITY BY SEVERAL PHYTOAGGLUTININS HAVING DIFFERENT SUGAR-BINDING PROPERTIES. (E.) Tomita, M. (Fac. Pharmaceutical Sci., U. Tokyo, Japan), T. Kurokawa, T. Osawa, Y. Sakurai and T. Ukita. *Cann* 63(2):269-271, 1972.
- 2584 EFFECTS OF SV40 VIRUS ON THE CHROMOSOMES OF POIKILOTHERMIC CELLS (*GEKKO GEKKO*) CULTIVATED AT DIFFERENT TEMPERATURES. (E.) Cohen, M. M. (Buffalo Med. Sch., N.Y.), H. F. Clark and F. Jensen. *Int J Cancer* 9(3):618-625, 1972.
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- 2587 IMMUNOFLOUORESCENCE OF ARGININE DEPRIVED CELLS INFECTED WITH ADENOVIRUS TYPE 12. (E.) Lefkowitz, S. S. (Med. Coll. Georgia, Augusta) and C. Y. Hung. *Experientia* 28(4):464-465, 1972.
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- 2595 RADIATION RESISTANCE OF THE MURINE MAMMARY GLAND TUMOR VIRUS SUBJECTED TO  $\gamma$ -RADIATIONS. (Fr.) Mouriquand, J. (Nucl. St. Ctr., Cell. Biol. Lab., Grenoble, France), C. Mouriquand, P. Mistry and C. Gorka. *C R Acad Sci [D] (Paris)* 274(15):2259-2262, 1972.
- 2596 INDUCTION OF VIRAL DEVELOPMENT IN CELLS DERIVED FROM PRIMARY MALIGNANT HUMAN ADENOPATHIES. (Fr.) Gevaudan, P. (Dept. Med., Marseille, France), G. Pieroni, M.-J. Gevaudan and J. Charrel. *C R Acad Sci [D] (Paris)* 274(13):1989-1991, 1972.
- 2597 HERPES-TYPE PARTICLES IN LYMPHOCYTES INFECTED WITH MAREK'S DISEASE AND MAINTAINED *IN VITRO*. (Fr.) Cauchy, L. (Natl. Inst. Agr. Res., Avian Path. Ctr., Tours, France) and F. Coudert. *C R Acad Sci [D] (Paris)* 274(12):1864-1866, 1972.
- 2598 AUTORADIOGRAPHIC STUDY OF BIOSYNTHESIS OF DNA, RNA AND PROTEIN IN CELL CULTURES INFECTED WITH HERPES SIMPLEX VIRUS. (Rus.) Dundarov, S. (Inst. Epid. Microbiol., Sofia, Bulgaria), B. Ivanov, P. Andonov and S. Todorov. *Vop Virus* 16(5):535-539, 1971.
- 2599 MECHANISMS INVOLVED IN NONGENETIC REACTIVATION OF FROG POLYHEDRAL CYTOPLASMIC DEOXYRIBOVIRUS: EVIDENCE FOR AN RNA POLYMERASE IN THE VIRION. (E.) Gravell, M. (St. Jude Children's Res. Hosp., Memphis, Tenn.) and T. L. Cromeans. *Virology* 46(1):39-49, 1971.

2600 THE DIFFERENTIATION OF HERPES SIMPLEX VIRUS  
TYPE I AND TYPE 2 BY TEMPERATURE MARKERS.  
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TWO INBRED STRAINS OF RATS. (E.) Borum, K. (Inst.  
Path., U. Lund, Sweden). *Lymphology* 4(4):150-155,  
1971.

## See also:

- \* (Rev): 2201, 2205, 2206, 2208, 2235, 2236,  
2237, 2238, 2239, 2241, 2253, 2256,  
2257, 2259, 2261, 2292
- \* (Chem): 2315, 2415, 2419
- \* (Phys): 2476
- \* (Immun): 2604, 2609, 2612, 2624, 2625, 2639,  
2644, 2647, 2655, 2672, 2694, 2699,  
2712



- 2602 DEVELOPMENT OF VARIANT TUMOR CELLS OF YOSHIDA ASCITES SARCOMA PRODUCING  $\alpha$ -FETOPROTEIN. (E.) Isaka, H. (Sasaki Inst., Hokkaido U., Sapporo, Japan), S. Umehara, H. Hirai and Y. Tsukada. *Gann* 63(1):63-71, 1972.

Tumor cells were taken from a Donryu rat bearing a four day old Yoshida ascites tumor of the 1,515th transplant generation. Cells were established in culture and some were treated with mutagens, including 4-nitroquinoline 1-oxide (4-NQO), nitrogen mustard, and N-methyl-N'-nitro-N-nitrosoguanidine. Control (i.e., not mutagen-treated) and treated Yoshida sarcoma cells were transplanted back to normal Donryu rats. Serial i.p. transplantations were made with the ascites of 17 rats of 76 tumor-bearing animals. Fourteen of these 17 transplant cell lines were examined for  $\alpha$ -fetoprotein production. Three lines (SB-7-2, UP and UO) showed  $\alpha$ -fetoprotein production. SB-7-2 and UO were derived from control Yoshida cells and UP was derived from 4-NQO-treated Yoshida cells. The three variant cell lines showed a slower growth tempo, as revealed by a longer survival time of host rats, than the original Yoshida sarcoma. The modal chromosome numbers of the SB-7-2, UP and UO cells were 93, 80 and 83, resp., while the modal number of chromosomes in the original Yoshida sarcoma cells was 40. The three variant cell lines were dissimilar in karyotype, especially in the number of chromosomes of the same type possessed by the three variant cell lines.

- 2603 CELL-MEDIATED RESPONSES TO TUMOUR XENOGRAFTS IN MICE. (E.) Simpson, E. (Clin. Res. Ctr., Harrow, England) and P. C. L. Beverley. *Int J Cancer* 9(2):299-304, 1972.

A micro-cytotoxic assay has been used to follow the course of the cell-mediated response to a tumor xenograft in normal and antilymphocyte serum (ALS) treated CBA mice. In normal mice, the lymph-node response is monophasic, suggesting that immune cells leave the node after day ten. In the spleen, further peaks of cytotoxic activity were seen at days 18 and 42. In ALS-treated mice, in which the tumor grew progressively, the response was slightly delayed in both lymph nodes and spleen. Subsequently ten out of 12 mice bearing progressively growing tumors, testing at times up to 83 days after tumor grafting, showed immunity in either lymph nodes, spleen or both.

- 2604 DEMONSTRATION OF CYTOTOXIC ANTIBODIES IN RABBITS BEARING TUMORS INDUCED BY SHOPE FIBROMA VIRUS. (E.) Singh, S. B. (Baylor Coll. Med., Houston, Tex.), J. W. Smith, W. E. Rawls and S. S. Tevethia. *Infect Immun* 5(3):352-358, 1972.

Rabbit kidney cells (RK-13) were infected with Shope fibroma virus (one or two infectious U/cell) for 48 hr. Cells were labeled with  $^{51}\text{Cr}$  during the last 12 hr of incubation with virus, and labeled cells were mixed with undiluted immune serum from rabbits whose Shope virus-induced fibromas had

regressed. Cytotoxic activity of immune serum for infected cells was investigated by the  $^{51}\text{Cr}$ -release test; cytotoxicity of test serum was expressed as per cent specific  $^{51}\text{Cr}$  released after six hr of incubation of labeled infected cells, serum, and guinea pig serum complement. There was a 75% specific release of radioactivity from virus-infected cells in the presence of immune serum and complement. The immune sera reacted only with fibroma virus-infected cells and not with cells infected with vaccinia virus or herpesvirus type 1. Similarly, sera against vaccinia and herpesvirus type 1 were not cytotoxic for fibroma virus-infected cells, although they were cytotoxic for cells infected with homologous viruses indicating that the immune response is specifically directed to antigen(s) specified by the fibroma virus. Rabbits inoculated i.d. with Shope virus were serially bled on days 3, 7, 13, 17, 23, 30 and 50 postinoculation, and their sera were tested for specific cytotoxicity against Shope virus-infected cells. Cytotoxic antibody in sera was demonstrated seven days postinfection and reached a maximum level on day 23, thereafter remaining constant through day 50. Rabbit immune sera collected on days 7, 13, 17 and 50 after virus infection were subjected to Sephadex G-200 chromatography and the fractions under 19S and 7S peaks were tested for cytotoxic antibodies. The 7S antibody response was maximal on day 13 postinfection and remained high for at least 50 days. The 19S antibody was detectable in sera collected on day 7 postinoculation, reached its maximum on day 13 and was barely detectable in sera collected on day 17. Tumors appeared in virus-inoculated rabbits on day 3 postinoculation, reached maximum size on day 13 and regressed completely by day 23.

- 2605 SPECIFIC KILLING OF TUMOR CELLS *IN VITRO* IN THE PRESENCE OF NORMAL LYMPHOID CELLS AND SERA FROM HOSTS IMMUNE TO THE TUMOR ANTIGENS. (E.) Pollack, S. (U. Washington Med. Sch., Seattle), G. Heppner, R. J. Brawn and K. Nelson. *Int J Cancer* 9(2):316-323, 1972.

Experiments are described which indicate that heat-decomplemented sera taken from mice 8-12 days after Moloney sarcoma virus (MSV) inoculation mediate a specific cytotoxic effect to Moloney sarcoma cells *in vitro* in the presence of normal lymphoid (lymph node) cells. Target neoplastic cells, sera, and non-sensitized lymphoid cells were taken from BALB/c and A/Sn strains of mice bearing, resp., MSV-induced sarcomas and an early transplant generation of a 3-methylcholanthrene (MCA)-induced sarcoma. Colony inhibition tests and microcytotoxicity tests were used to test for interaction of target cells, sera and lymphoid cells. In the case of the MSV- and MCA-induced sarcomas, there was a marked growth-retarding and/or cytotoxicity effect on neoplastic target cells in the presence of non-sensitized lymphoid cells and heat decomplemented serum from mice bearing the corresponding tumors. The presence of non-sensitized lymphoid cells was required for the cytotoxic effect. This effect was tumor-specific in that the presence of non-sensitized lymphoid cells and sera from animals bearing a tumor other than

that from which the target cells were taken did not inhibit neoplastic target cell growth. Killing of neoplastic cells was also found when murine mammary adenocarcinoma target cells were mixed with sera and non-sensitized lymphoid cells from mice whose autochthonous or transplanted mammary tumors had been surgically removed.

- 2606 IMMUNOLOGIC STUDIES OF THE AVIAN MYELOBLASTOSIS RNA VIRUS. (Fr.) Verger, C. (Gustave-Roussy Inst., Villejuif, France), E. Nahon-Merlin and F. Lacour. *C R Acad Sci [D] (Paris)* 274(16): 2391-2394, 1972.

The avian myeloblastosis virus (AMV) was studied by means of anticomplex immune sera of polyribonucleotides which react with nucleic acids. The poly G.-poly C immune serum reacts specifically only with ribosomal RNA from animal cells and with some viral RNA (Reovirus RNA, bacteriophage Q beta RNA), but does not precipitate the 70 S (heavy) fraction of AMV. The reactions of various RNA fractions with anticomplex polynucleotide immune sera were followed by the double diffusion method in gelatin with the RNA used labeled with P-32, and by a radioimmunological technique which brings into contact the agar containing the immunological precipitates with a photographic emulsion. The radioactive ribosomal RNA and the transfer RNA were isolated from mouse FLS ascites tumor cells labeled for 4 hours with P-32, and sedimentation curves of the radioactive RNA from the AMV and of the radioactive transfer RNA from mouse ascites tumor cells were established. The light RNA fractions from AMV with a sedimentation constant lower than 30 S contained RNA with immunological properties similar to those of ribosomal RNA.

- 2607 INTERACTION BETWEEN SUBCUTANEOUS AND INTRA-PERITONEAL TRANSPLANTS OF THE EHRlich CARCINOMA; THE POSSIBLE ROLE OF ANTI-TUMOUR ANTIBODY. (E.) Halleraker, B. (Gade Inst., U. Bergen, Norway) and F. Hartveit. *J Path* 105(2):95-103, 1971.

The electrophoretic mobility of Ehrlich ascites carcinoma cells grown in the presence of a late (105-day) s.c. transplant of the same tumor was higher than that in mice with early (17-day) s.c. transplants, and higher than that of comparable tumor cells from mice without a s.c. transplant. These tumor cells with a high electrophoretic mobility may lack the antibody coating that is usually acquired by Ehrlich cells grown in untreated mice. The finding that the tumor cells retained the appearance characteristic of tumor cells from an early i.p. transplant throughout the period investigated, and at 10 days, unlike control cells, failed to establish an acute inflammatory response on re-transplantation into normal mice, supports the hypothesis that the late subcutaneous transplant may act as a sponge, mopping up antibody and so leaving little available to coat the cells of a subsequent transplant.

- 2608 HL-A ANTIGENS IN MALIGNANT DISEASES. (E.) Jeannet, M. (U. Hosp., Geneva, Switzerland), and C. Magnin. *Transplantation Proc* 3(3):1301-1303, 1971.

One hundred and forty-seven patients with malignant diseases were typed for 22 well defined HL-A antigens. The group included 26 patients (mainly children) with acute lymphoblastic leukemia (ALL), 25 patients (mainly adults) with acute myeloblastic leukemia (AML), ten with chronic myelocytic leukemia (CML), 15 with chronic lymphocytic leukemia (CLL), 33 with Hodgkin's disease, 11 with other malignant lymphomas of various histological classes, and 27 with cancer, mainly of the lung and the breast. Typing was performed by the Terasaki lymphocytotoxic microtechnique assay. Each patient was typed for 22 HL-A antigens. The frequency of each HL-A antigen was compared among the patients with hematological malignant diseases and among 305 healthy individuals. Only two antigens were found which showed a significantly different frequency in patients with hematologic malignant diseases as compared to that in the normal population. The HL-A 11 antigen which has a frequency in the normal population of 16% was present in the cells of only three patients, a frequency of 2% ( $p < 0.001$ ). W22, which has a frequency of 7% in the normal population was found positive only twice ( $p < 0.05$ ). When each specific hematological malignant disease was considered separately, other HL-A antigens were found to differ significantly in frequency when compared with the group of normal individuals.

- 2609 ANTIBODIES TO A NEW ANTIGEN INDUCED BY EPSTEIN-BARR VIRUS IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA, LEUKEMIA, MALIGNANT LYMPHOMA, AND IN CONTROL GROUPS. (E.) Ida, S. (Tohoku U. Sch. Dentistry, Japan), T. Sairenji and Y. Hinuma. *Gann* 63(1):49-55, 1972.

Sera from Taiwan Chinese and Japanese patients with nasopharyngeal carcinoma (57 patients), leukemia (61 patients), malignant lymphoma (52 patients), "other neoplasms" (102 patients) and infectious mononucleosis (19 patients) were examined to determine the titer of antibody to the non-virion N antigen, an antigen induced by Epstein-Barr virus. Normal sera from healthy donors were also examined. Antibody to the anti-virion V antigen was also titrated in these sera. The titers of anti-N antibody and anti-V antibody were determined by indirect immunofluorescence. Seventy-two percent of nasopharyngeal carcinoma patients had anti-N titers  $\geq 1:10$ . Fifteen percent of leukemia patients had anti-N titers  $\geq 1:10$ . Seventeen percent of patients with "other neoplasms" (including stomach, pancreas and lung carcinoma, leiomyosarcoma, Wilm's tumor, neuroblastoma and others) had anti-N titers  $\geq 1:10$ . Five percent of infectious mononucleosis patients and less than 1% of healthy donors had anti-N titers  $\geq 10$ . Forty-four percent of sera with anti-N gave anti-V titers in the normal range ( $\leq 1:160$ ) and only 4% of sera



with negative anti-N titers from patients with other neoplasms had a high titer of anti-V ( $\leq 1:320$ ).

- 2610 IMMUNOLOGICAL STUDIES ON MOUSE MAMMARY TUMORS: VI. FURTHER CHARACTERIZATION OF A MAMMARY TUMOR ANTIGEN AND ITS DISTRIBUTION IN LYMPHATIC CELLS OF ALLOGENEIC MICE. (E.) Chang, S. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan), R. C. Nowinski, K. Nishioka and R. F. Irie. *Int J Cancer* 9(2):409-416, 1972.

Properties of a cross-reacting antigen found in ascitic mammary tumors of C3H/He mice and in lymphatic cells of mice of other strains are described. The characterization of this antigen (designated MM) in allogeneic mice was of especial interest. MM-102, an ascitic form of C3H/He mammary tumor, was used as a standard cytotoxic test cell characterizing the antibody against the MM antigen. MM antigen was not present in normal cells of C3H/He mice. MM antigen appeared as an alloantigen in mice of the following strains: C57BL/6, AKR, C58, 129, C57L, H-2H, 101, RF, SJL/J and Swiss. The reactivity of anti-MM-102 serum with various experimental tumors was examined. Spontaneous leukemias and mammary tumors of Swiss mice, leukemias of C57BL/6 mice (including the EL4 leukemia), and spontaneous mammary tumors of DBA/2 mice were among tumors found to react with anti-MM-102 serum. Various tissues of C57BL/6 mice were tested for distribution of the MM antigen. MM antigen was most abundant in lymphocytes and was also present in thymocytes and spleen cells, but the antigen was never detected in red blood cells, liver, or other organs. The MM antigen was apparently controlled by a dominant gene independent of any known allo-antigen. The gene locus for the MM antigen was designated MMA. The MM antigen resembled the TL antigen in that MM appeared as an alloantigen in lymphatic cells of mice of many strains. The striking difference between MM and TL was that the TL antigen does not act as a transplantation antigen, while MM had previously been shown to act strongly as a transplantation antigen.

- 2611 INDIVIDUALLY SPECIFIC ANTIGENIC DETERMINANTS SHARED BY A MYELOMA PROTEIN AND NONSPECIFIC IgG. (E.) Wilson, S. K. (U. Illinois Coll. Med., Chicago), B. W. Briant and A. Nisonoff. *Ann New York Acad Sci* 190:362-370, 1971.

Individually specific antigenic determinants of certain myeloma proteins, present in low concentrations in nonspecific IgG, were examined. Cross-reactions, with nonspecific IgG and with other myeloma proteins, of antibodies directed to individually specific determinants of a human myeloma protein, were studied. The inhibition of the direct precipitation reaction of IgG from a myeloma patient (Til IgG) with rabbit anti-Til IgG, and the inhibition of binding of labeled F(ab')<sub>2</sub> fragments of Til IgG by rabbit anti-Til IgG antibodies in the presence of unlabeled nonspecific IgG or unlabeled heterologous myeloma proteins, were

observed. High concentrations (20 or 40 mg/ml) of pooled nonspecific human IgG could completely inhibit the direct precipitation of Til IgG with a rabbit antiserum to its individually specific antigenic determinants. After absorption with low concentrations (1 mg/ml) of nonspecific IgG, the antiserum still formed precipitants with Til IgG, but not with any of more than 30 other myeloma proteins or sera tested, indicating that the inhibitory effect was largely restricted to non-specific human IgG. Evidently, the individually specific antigenic determinants of Til IgG have similar or identical counterparts present in low concentrations in nonspecific IgG but not in most other myeloma proteins. Nonspecific human IgG had no measurable effect on the binding of <sup>125</sup>I-F(ab')<sub>2</sub> fragments of Til IgG by antibodies directed to individually specific determinants. Studies of idiotypic determinants on rabbit antihapten antibody were performed using a quantitative technique. Specific haptens inhibited the interaction of anti-p-azobenzoate antibody with its antiidiotypic antibody. The findings, taken together, were thought to suggest that the unique determinant on certain myeloma proteins may be in the region of the antigen-binding site of the molecule.

- 2612 ANTIBODY TO FELINE ONCORNAVIRUS-ASSOCIATED CELL MEMBRANE ANTIGEN IN NEONATAL CATS. (E.) Essex, M. (Karolinska Inst., Stockholm, Sweden), G. Klein, S. P. Snyder and J. B. Harrold. *Int J Cancer* 8:384-390, 1971.

A positive correlation was found between the presence of antibody against a feline oncornavirus-associated cell membrane antigen in neonatal kittens and the ability of the kittens to resist the development of progressive tumors. Kittens which were born of mothers with no known exposure to feline sarcoma virus (FSV) or feline leukemia virus (FeLV), and kittens born of mothers which, 6-12 months earlier, had nursed litters of kittens injected with FeLV, were injected with FSV during the first 2-8 days of life. Kittens from dams which had nursed FeLV-treated litters had an increased ability to resist development of progressive FSV-induced tumors; four of 16 such kittens developed tumors after FSV-treatment, while 11 of 13 kittens of mothers not previously exposed to FeLV developed tumors. In the group whose mothers had been exposed to FeLV, indirect immunofluorescence tests showed that nine of 19 kittens had antibody against the feline oncornavirus-associated cell membrane antigen. However, none of 19 kittens from dams not exposed to FeLV had detectable antibody. That the mothers were able passively to transmit immunity suggests that mothers became infected with FeLV in a horizontal manner while nursing previous litters and resisted the development of progressive tumors, but mounted an immune response which resulted in the production of humoral antibody.

- 2613 HIGH-FREQUENCY ESTABLISHMENT OF HUMAN IMMUNOGLOBULIN-PRODUCING LYMPHOBLASTOID LINES FROM NORMAL AND MALIGNANT LYMPHOID TISSUE AND

th: PERIPHERAL BLOOD. (E.) Nilsson, K. (Wallenberg  
in: Lab., U. Uppsala, Sweden). *Int J Cancer* 8:432-442,  
ne: 1971.

ad Attempts to establish continuous human lymphoblastoid  
no cell lines (LL) from solid lymphoid tissue (lymph  
ch nodes, spleen, bone marrow) and from peripheral  
su blood lymphocytes are reported. Biopsy specimens  
and blood samples for culture were taken from non-  
cancer patients and from cancer patients. Two types  
of grid organ culture were used, lens-paper grid  
culture and Spongostan (gelatin foam) grid culture.  
26 Permanent LL were successfully established from 21 of  
22 lymph node biopsies from adult patients with non-  
malignant conditions, from one nonmalignant spleen  
biopsy, from two of four lymph nodes from cancer  
23 patients, and from three of six malignant bone  
marrows. LL were also established from blood  
cultures from four of ten non-malignant donors, and  
The from five of 19 cancer patients. All LL produced  
me immunoglobulins. Some LL secreted only one class of  
ti heavy and one of light chain immunoglobulin, others  
po showed a "polyclonal" pattern of immunoglobulin  
ri production initially but changed to a "monoclonal"  
RN pattern with increased time in culture. The  
no successful establishment of 21 LL from 22 non-  
re malignant biopsies was unexpected. It is believed  
po that a potential for infinite growth is the  
di common property of human lymphoid tissue, non-  
wh malignant as well as malignant.

2614 PART V. ACTIVE SITES OF ANTIBODIES:  
AFFINITY LABELING OF THE ACTIVE SITES  
OF ANTIBODIES AND MYELOMA PROTEINS. (E.) Singer,  
S. J. (Dept. Biol., U. California, San Diego),  
ce N. Martin and N. O. Thorpe. *Ann N Y Acad Sci*  
fr 190:342-351, 1971.

The theoretical aspects of affinity labeling are  
discussed, including stereospecificity of labeling  
reaction, multiplicity of affinity-labeled residues  
and whether or not the affinity-labeled residue is  
26 present in the active site. In a discussion of the  
affinity labeling of some antibenzoic hapten  
CA antibodies with specific diazonium reagents, it was  
(E shown that in each case, the reaction was specific  
an and directed to the active site, as verified by the  
fact that in the presence of a reversible protector  
of the sites, the extent of labeling reaction was  
Th significantly reduced. It is concluded that the  
ci affinity-labeled residues are contact residues  
s. in the active sites. Affinity labeling has also been  
in applied to some myeloma proteins with ligand-binding  
er capacity. In a study of the affinity labeling of  
ot DNP-binding mouse IgA myeloma protein MOPC-315 with  
hi the reagent 3H-MNBDF, it was shown that specific  
cc labeling did occur, that it was confined to tyrosine,  
gr and that L-chain carried 85% or more of the label.  
ti Subsequently the predominant labeled residue in the  
of L-chain was shown to be tyrosine-34. In the  
ot authors own studies with ligand-binding myeloma  
cc proteins, they examined an IgG2a myeloma, HPC-3,  
m: with DNP-binding activity isolated from NZB mice  
m: and found it to affinity-label with 3H-MNBDF, with  
ti most of the specific affinity label being found on  
ai the H chains and attached to tyrosine. The small  
tl

amount of label detected on the unprotected L-  
chains also appeared to be specific to the active  
site. (32 references)

2615 IMMUNOSUPPRESSIVE PROPERTIES OF ACRIDINE  
AND ACRIDONE DERIVATIVES. (E.) Geldan-  
owski, J. (Polish Acad. Sci., Wroclaw), B. Szaga, J.  
Patkowski and A. Pelczarska. *Arch Immun Ther Exp*  
19(4):465-483, 1971.

Acridine and acridone derivatives, including 1-  
nitro-9-(methylamino)-acridine (AK-1), 1-nitro-9-(3-  
diethylaminoethylamino)-acridine (AK-2), 1-nitro-9-  
(3-dimethylaminopropylamino)-acridine (AK-3), 1-  
nitro-9-(3-diethylaminopropylamino)-acridine (AK-4)  
and 1-nitro-9-(3-dimethylaminopropylamino)-acridone  
(AK-5) were studied immunopharmacologically *in vivo*.  
Rabbits, guinea pigs, rats, and mice were given i.v.  
injections of one of the above-named compounds on  
two consecutive days prior to antigenic stimulation  
and then every other day thereafter until the end of  
the experimental period. The extent of antibody  
reaction was determined by nine different biochem-  
ical or histologic tests. Precipitin production,  
tuberculin-type hypersensitivity, and contact  
sensitivity were all unaffected by any of the de-  
rivatives. Production of anaphylactic antibodies,  
on the other hand, was slightly inhibited by AK-2 in  
rabbits and by AK-1 and AK-2 in mice; AK-5, however  
clearly gave complete protection in mice. All the  
acridine derivatives suppressed transplantation  
immunologic responses as follows: AK-2 and AK-3  
affected responses in rats; AK-1 and AK-3, in rab-  
bits; and AK-1 and AK-4, in mice when the compounds  
were given over a long period of time. Acridine  
derivatives aided resistance to postadjuvant ar-  
thritis, particularly in rats where AK-2 gave com-  
plete and AK-3, slight, protection; the acridone  
derivative AK-5 caused significant lessening of  
articular symptoms, but only in rats. Histologic  
observations indicated that the spleen, lymph nodes  
liver, adrenals, and bone marrow were all affected  
by the derivatives. Specifically, all of the compounds  
except AK-3 caused microscopic changes in tissue,  
such as lipid deposits, proliferation of connective  
tissue, fluctuations in specific white blood cell  
levels, and general increase in lymphocytes and  
macrophages. In summary, preparations with an acri-  
dine ring may be a basis for the development of  
immunosuppressive drugs, especially in the suppres-  
sion of immunologic processes associated with infla-  
mmatory reactions.

2616 THE IMMUNOGENIC ACTIVITY OF TUMOR ANTI-  
GENS RETAINED BY THE RETICULOENDOTHELIAL  
CELLS OF TUMOR-BEARING MICE. (E.) Vaage, J. (U.  
Texas, Houston). *Cancer Res* 32(5):898-903, 1972.

Radiation-killed, <sup>3</sup>H-alanine-labelled tumor cells  
were injected into the centers of growing s.c.  
fibrosarcoma and mammary carcinomas implanted in  
12-wk-old female C3H/Bu mice. Groups of three  
mice each were studied by autoradiography and liq-  
uid scintillation counting to localize labeled com-



ponents disseminated from the tumor, and it was found that most of the labelled components were retained in the liver. The radioactive label was lost more rapidly from the liver than from other sites after the tumor containing the labelled tumor cells was removed. It was found that livers of mice with a highly antigenic tumor had factors which were very active immunogens; these factors were most active in mice presensitized with tumor antigen in the form of killed cells and were ineffective, by themselves, for initiation of antitumor immune resistance as detectable by the assay methods used.

- 2617 RENAL TUBULAR ANTIGENS IN KIDNEY TUMORS. (E.) Wallace, A. C. (Monash U. Med. Sch., Melbourne, Australia) and R. C. Nairn. *Cancer* 29(4):977-981, 1972.

Immunofluorescent studies of renal cortical adenomas, renal cell carcinomas, and Wilms' tumors were performed using two antisera, one which reacted with the brush border of proximal convoluted tubules (BB) and the other which reacted with Tamm-Horsfall protein in distal convoluted tubules and loops of Henle (TH). Normal kidneys, tumors and other tissues were studied by sandwich immunofluorescence, using fluorescein-labelled goat anti-rabbit globulin (mainly anti-IgG) absorbed with normal tissue homogenates until, by itself, it gave no staining of the microscope preparations. The BB antiserum reacted with all the renal cortical adenomas and renal cell carcinomas except for the single anaplastic carcinoma. No adenomas or clear cell carcinomas reacted with the TH antibody. Both Wilms' tumors showed tubular structures that stained individually with either the BB or TH antiserum but not with both. These results furnish further evidence that renal cortical adenomas and renal cell carcinomas arise from proximal convoluted tubules, since they have antigen not found elsewhere in normal kidney.

- 2618 STUDIES ON NITROSODIMETHYLAMINE: PREFERENTIAL METHYLATION OF MITOCHONDRIAL DNA IN RATS AND HAMSTERS. (E.) Wunderlich, V. (Inst. Cancer Res., German Acad. Sci., Berlin-Buch), I. Tetzlaff and A. Graffi. *Chem-Biol Interactions* 4(2):81-89, 1972.

Male Wistar rats and male and female random-bred Syrian hamsters were given single i.p. injections of the nitroso carcinogen, *N*-nitroso-[<sup>14</sup>C]-dimethylamine (DMNA), and after five hr radioactive 7-methylguanine was eluted from hydrolysates of nuclear and mitochondrial (mt) DNA purified from their liver and kidney homogenates and measured. The mt DNA from both liver and kidney was labeled two to eight times as much as was the nuclear DNA. Small quantities of pyrimidine deoxynucleotides, guanine and adenine were labeled, but 7-methylguanine (82.6% of mtDNA radioactivity) was the predominant methylation product in both nuclear and mtDNA. Both DNA species of liver were labeled three to seven times higher than those of kidney

due to the fact that DMNA is primarily metabolized in liver. The extent of methylation of DNA from hamster liver and kidney was higher than that of DNA of the corresponding rat tissues. It is concluded that mtDNA is preferentially methylated by DMNA and that therefore cytoplasmic mutations may be involved in carcinogenesis.

- 2619 HUMORAL CROSS IMMUNITY IN PATIENTS WITH MALIGNANT TUMORS. (E.) Harlozinska, A. (Polish Acad. Sci., Wroclaw), Z. Albert, R. Richter, Z. Singer and J. Salwa. *Arch Immun Therap Exp* 19:835-849, 1971.

The antigenic relationship and specific antitumor cross immunity between histologically related groups of human tumors are studied. A total of 46 different malignant tumors were examined and divided into four groups: 1) breast carcinoma; 2) digestive tract tumors; 3) lympho- and reticulosarcomas; and 4) acute myeloid leukemia. Tumor tissue, bone marrow and peripheral blood smears were obtained from the patients. Antigenic specificity and antitumor cross immunity were determined by indirect immunofluorescent techniques, with rabbit anti-human globulin labeled with isothiocyanate used as the immunohistochemical reagent. Tests were performed by cross reactions between tumor preparations and the patients own serum and with the sera of other patients with the same histological type of tumor. A control series was carried out on various target cells from tissues of healthy patients. In 19 cases of breast cancer, 10 positive reactions were obtained with the patient's own serum. No positive reactions were observed in 22 control tests with sera of healthy patients. In the group of digestive tract tumors, 12 positive results occurred in 53 cross tests. When tumors of the hemopoietic system were examined in 72 cross tests with 31 sera of patients with similar proliferative diseases, 26 positive results were obtained. Small numbers of positive results were obtained from cases of acute leukemia; this was thought to be due to the poor clinical condition of the patients themselves. Results of the testing program indicate that antigenic specificity seems to be dependent on the character of the tumor-inducing factors and biologic properties of the particular groups of human tumors.

- 2620 RESISTANCE OF GUINEA PIGS TO LEUKEMIA FOLLOWING TRANSFER OF IMMUNOCOMPETENT ALLOGENEIC LYMPHOID CELLS. (E.) Katz, D. H. (Natl. Inst. Allergy Infec. Dis., Bethesda, Md.), L. Ellman, W. E. Paul, I. Green and B. Benacerraf. *Cancer Res* 32(1):133-140, 1972.

This report describes an experimental approach for the development of tumor protection based on stimulation of host immune response following induction of a transient graft *versus* host (GVH) reaction. Lymph nodes and spleen from strain 13 guinea pigs were prepared as a cell suspension and  $1.0 \times 10^9$  of these cells were inoculated i.v. into allogeneic strain 2 guinea pigs. The strain 2 guinea pigs were

then given transplantations of guinea pig L<sub>2</sub>C leukemia cells. Results showed that a crucial temporal relationship existed between the transfer of allogeneic cells and the administration of lethal L<sub>2</sub>C leukemia cells. Highly significant protection was observed in guinea pigs that received allogeneic cells 1, 3, or 6 days prior to the leukemia cell challenge. A striking prolongation of animal survival time was seen in essentially all strain 2 guinea pigs even when doses of L<sub>2</sub>C cells were 30-fold higher than lethal dose. Protection was not afforded when allogeneic cells were received 21 days, or immediately, before challenge. The results are considered significant in light of the critical cellular action by the host cell population which seems to have been highly stimulated by events occurring in the initial GVH reaction. Actions occurring here indicate a heightening of cell immunological memory as well as antibody synthesis.

- 2621 CARCINOEMBRYONIC ANTIGEN IN FAECES. (E.) Freed, D. L. J. (Dept. Bact., U. Manchester, England) and G. Taylor. *Brit Med J* 1(5792):85-87, 1972.

A possible technique for quantitative demonstration of carcinoembryonic antigen (CEA) a protein, polysaccharide complex which is present in epithelial cell membranes of fetal gastrointestinal structures, disappears at about six months' gestation and in the adult is found in adenocarcinoma of the gastrointestinal tract, is presented. Since there is a high turnover of epithelial cells in the intestinal tract, an examination of the CEA content in feces of 18 patients with gastrointestinal cancer was compared to that of 23 non-neoplastic individuals. Bowel tissue specimens from cancerous, normal and fetal subjects were prepared as homogenates, after freeze-dry extraction reconstitution of tissue was achieved by immersion in distilled water at concentrations of 10 mg/ml for tissue and 25 mg/ml for feces. Samples were tested against absorbed rabbit antiserum by double diffusion in 1% agar gel at pH 7.3. Results showed that completely absorbed sera produced a single line on gel immunodiffusion against extracts of 17 of the 18 tumor tissues but against only one of the 11 normal tissues. All extracts from fetal tissue contained detectable CEA. In feces samples, CEA was detected in ten of 11 patients with colonic cancer and in five of ten normal patients, suggesting that cancer, polyposis coli or residue fetal tissue might exist in the normal patients. Recommendations for development of a more sensitive CEA assay technique are made with the goal of defining "normal limits" for CEA content in feces.

- 2622 INCREASED ONCOGENIC EFFECT OF A LOW DOSE OF METHYLCHOLANTHRENE IN IMMUNODEPRESSED MICE. (E.) Carbone, G. (Inst. Cancer Res., Philadelphia, Pa.) and G. Parmiani. *Tumori* 57(4): 225-231, 1971.

The effects of two low doses of 3-methylcholanthrene (MCA) on the development of sarcomas in immunodepressed and intact mice were compared. Thirty-six female (C57BL/6xBALB/c)F<sub>1</sub> mice were thymectomized at

ten wk of age and two wk later received i.p. antilymphocyte serum (ALS) injections in 0.25 ml doses on days -1, +1, +3, +5, resp. These immunodepressed mice were divided into two groups of 18 each; on day 0, one group received s.c. implantations of 30 µg MCA in paraffin and the other, 150-µg of the carcinogen in paraffin. The group of 36 intact mice also received MCA implantations, but no injections of ALS. The results indicated that the 30-µg dose of MCA gave rise to sarcomas in 11 of 18 intact mice, and in all of the immunodepressed animals, whereas with the 150-µg dose groups, 16 of 17 immunodepressed and 17 of 17 intact counterparts developed tumors. These results point up the importance of dosage in the function of immunologic surveillance in this system of chemical carcinogenesis.

- 2623 ANTILYMPHOCYTIC SERUM AND TUMOUR TRANSPLANTATION IN THE BRAIN. (E.) Ridley, A. (Inst. Neurol., London, England). *Acta Neuropath* 19(4):307-317, 1971.

The use of antilymphocyte serum (ALS) to enhance tumor transplantability has been applied to the study of transplantable hamster brain tumors. Neither polyoma virus-induced spindle cell sarcoma nor estrogen-induced kidney tumor could successfully be transplanted into WAG/C rat brains unless immune response was eliminated in the animals by simultaneous treatment with ALS. Rats given single s.c. injections of these two tumors, and immediately started on 100 ml/kg ALS thrice weekly, in the case of the estrogen tumor and in the case of the polyoma tumor on alternate days, developed large nodules occupying most of the inoculated cerebral hemisphere by the 16<sup>th</sup>-19<sup>th</sup> day. Attempts to transplant human glioma tissue were unsuccessful, even with ALS treatment. Of five rats inoculated with grade 3 glioma, two showed malignant-appearing cells at the implantation site, but these cells could not definitely be identified as glioma cells.

- 2624 VIRUS-CODED ANTIGENS IN CHEMICALLY INDUCED LEUKEMIA. (E.) Pasternak, G. (German Acad. Sci. Berlin-Buch) and L. Pasternak. *Boll Inst Sieroter Milan* 50(3):192-198, 1971.

Immunofluorescence and immunodiffusion techniques were used to characterize the antigens of leukemia induced by methyl nitrosourea (MNU) in mice (XVII, CBA, AKA and (XVII X AKR)F<sub>1</sub> hybrid strains). MSU was injected s.c. into newborn mice; 50% developed leukemia after a mean latency period of 120 days. Challenge inoculation of the mice with the tumor with which they had been previously immunized with x-ray-killed cells resulted in a significant decrease of tumors (43.5% compared to 85.9% of the controls,  $p < 0.0005$ ). It was therefore concluded that MNU-induced leukemia had tumor-specific transplantation antigen (TSTA). No cross immunity was observed for five different MNU leukemias. Preimmunization with Gross leukemia did not confer resistance to MNU leukemia *in vivo*. When MNU leukemia cells were tested *in vitro* with Graffi and Gross immune sera,



a high proportion gave a positive reaction, indicating the presence of group-specific surface and viral antigens. A positive result for the membrane fluorescent antibody test did not always correlate with a similar result for the immunodiffusion test and vice versa. Four types of MNU leukemia were distinguished on the basis of these findings.

2625 IMMUNOLOGICAL INTERFERENCE WITH ROUS SARCOMA VIRUS TUMORIGENESIS IN RATS.

(E.) Jonsson, N. (Inst. Path., U. Lund, Sweden). *Acta Path Microbiol Scand* 79:584-590, 1971.

A study to clarify whether a "specific" prophylactic effect in Rous rat system can be obtained by means of treatment with irradiated Rous tumor cells or with lymphoid cells derived from donors immunized against such cells is reported. Rats, inoculated when newborn with Rous sarcoma virus (SR-RSV), were inoculated with irradiated syngeneic Rous tumor cells or with syngeneic lymphoid cells from specifically immunized donors. Treatment with irradiated tumor cells gave no demonstrable protection, while administration of specific immune lymphoid cells before and in some experiments a few days after SR-RSV inoculation had a protective effect. Together with the fact that both tumor-negative and tumor-positive rats show a high degree of cell-mediated and humoral immunity the results indicate that the rapidity with which the cell-mediated immunity develops plays an important role for the progressive growth or elimination of the neoplastic cells.

2626 LEVELS OF IMMUNOGLOBULINS IN THE SERUM OF PATIENTS WITH CARCINOMA OF THE PROSTATE.

(E.) Ablin, R. J. (Southern Illinois U. Sch. Med., Springfield), M. J. Gonder and W. A. Soanes. *Neoplasma* 19(1):57-60, 1972.

Radial immunodiffusion, as described by Mancini et al, was used to determine the concentration (mg/100 ml) of the three major immunoglobulins (IgG, IgA and IgM) in 23 patients with carcinoma of the prostate. Serum of 22 healthy adults were used as controls. A significant decrease in the levels of IgG ( $P < 0.01$ ) and IgM ( $P < 0.01$ ) contrasting with an increase in the level of IgA ( $P < 0.03$ ) in the serum of patients with carcinoma of the prostate, was demonstrated. In five of the 23 patients with carcinoma of the prostate, the IgA concentration ranged from 365.0 to 550.0 mg/100 ml.

2627 LOCALIZATION OF  $\alpha$ -FETOPROTEIN IN HEPATOMA TISSUES BY IMMUNOFLOUORESCENCE. (E.)

Nishioka, M. (Yamaguchi U. Sch. Med., Japan), T. Ibata, K. Okita, T. Harada and T. Fujita. *Cancer Res* 32(1):162-166, 1972.

An immunologic study of  $\alpha$ -fetoprotein (AFP) in hepatoma tissues is presented. Autopsy specimens,

obtained from ten patients with primary hepatocellular carcinoma and three patients with liver carcinoma metastasized from the stomach, were examined. Normal human livers obtained from autopsies of patients who had died of other diseases and livers from eight to 20-week-old fetuses, were tested as controls. All specimens were tested by a modification of the indirect fluorescent antibody method of Coons and Kaplan. One section of each liver specimen was stained with hematoxylin and eosin for the identification of structural localization. The Ouchterlony gel-diffusion technique was used to detect the serum AFP. The experiments showed the fluorescence of the tumor cells to appear in three forms: 1) diffuse, finely granular fluorescence of the cytoplasm, (this was the most common type), 2) fluorescent line of the cytoplasmic membranes and 3) brightly fluorescent line of the perinuclear zones. The immunofluorescent sintering was specific for AFP, failing to stain normal human liver controls. There was no correlation between the levels of serum AFP and the occurrence of fluorescence in the tumor cells, or between the occurrence of fluorescence and the histological gradings of primary liver carcinoma. The data show the tumor cells contain different amounts of AFP and that not all tumors cells contain AFP.

2628 PRESENCE OF EBV ANTIBODIES IN SERA FROM WILD CHIMPANZEES. (E.) Levy, J. A.

(Dept. Med., U. California, San Francisco), S. B. Levy, Y. Hirshaut, G. Kafuko and A. Prince. *Nature* 233(5321):559-560, 1971.

Sera from three wild chimpanzees in the Bodongo Forest in Western Uganda were tested for the presence of Epstein-Barr virus (EBV). The fluorescent antibody technique with fluorescent-labelled goat anti-human globulin and anti-monkey globulin was used after the chimpanzee sera were incubated with either the human P3 (Jiojoye) Burkitt lymphoma or the LE-7 chimpanzee lymphocyte cell line. Two of the three sera from the wild chimpanzees showed a positive reaction with both human and chimpanzee lymphocyte cells. Thus, these results indicated that these wild chimpanzees which had not been in contact with humans had been infected by EBV or a similar herpes-type virus. It is suggested that the presence of these antibodies show that wild chimpanzees and perhaps other primates in the area studied may help to spread EBV infection to man.

2629 CELL-TO-CELL INTERACTION IN THE IMMUNE RESPONSE: VII. REQUIREMENT FOR DIFFERENTIATION OF THYMUS-DERIVED CELLS. (E.)

Miller, J. F. A. P. (Hall Inst. Med. Res., Melbourne, Australia), J. Sprent, A. Basten, N. L. Warner, J. C. S. Breitner, G. Rowland, J. Hamilton, H. Silver and W. J. Martin. *J Exp Med* 134(5):1266-1284, 1971.

Experiments were designed to test the possibility that thymus-derived (T) cells cooperate with nonthymus derived (B) cells in antibody responses by acting as

passive carriers of antigen. Thoracic duct lymphocytes (TDL) from fowl  $\gamma$ G-tolerant mice were incubated *in vitro* with fowl anti-mouse lymphocyte globulin (FALG), which was shown not to be immunosuppressive in mice. On transfer into adult thymectomized, irradiated, and marrow protected (TxEM) hosts together with a control antigen, horse RBC, a response to horse RBC but not to fowl  $\gamma$ G was obtained. By contrast, TxEM recipients of nontolerant, FALG-coated TDL responded to both antigens and the antibody-forming cells were shown to be derived from the host, not from the injected TDL. These findings suggest that, under the conditions of the experiment, triggering of unprimed B cells in the spleens of TxEM hosts is not achieved with antigen-coated tolerant lymphocytes. Spleen cells from TxEM mice, incubated *in vitro* with anti-fowl  $\gamma$ G-fowl  $\gamma$ G-NIP, were injected with or without normal TDL (a source of T cells) into irradiated hosts. Only mice given both cell types could produce an anti-NIP antibody response. In a further experiment spleen cells from HGG-NIP-primed mice were injected together with NIP-coated B cells into irradiated hosts. A substantial anti-NIP antibody response occurred. When the T cells in the spleens of HGG-NIP-primed mice were eliminated by treatment with anti- $\theta$  serum and complement, the NIP response was abolished. It is concluded that antigen-coated B cells cannot substitute for T cells either in the primary or secondary response. Treatment of T cells from unprimed or primed mice with mitomycin C impaired their capacity to collaborate with B cells on transfer into irradiated hosts. Taken together these findings suggest that before collaboration can take place T cells must be activated by antigen to differentiate and in so doing may produce some factor essential for triggering of B cells.

- 2630 CARCINOEMBRYONIC ANTIGEN PRESENT IN HUMAN COLONIC NEOPLASMS SERIALLY PROPAGATED IN HAMSTERS. (E.) Hansen, H. J. (U. Hlth. Sci. Ctr., Philadelphia, Pa.) and D. M. Goldenberg. *Science* 175 (4026):1117-1118, 1972.

Two human, mucin-producing colonic tumors, GW-39 and GW-77, were implanted and grown in the cheek pouches of adult golden hamsters, excised, and analyzed for carcinoembryonic antigen (CEA) by radioimmunoassay. In tumor GW-39, 162  $\mu$ g/g CEA was found, and 41  $\mu$ g/g CEA was found in tumor GW-77. Thus, the capacity of these tumors to continue producing CEA after implantation into xenogeneic hosts shows that these antigens are tumor-specific and not the result of tumor-host interaction.

- 2631 ELEVATED LYMPHOCYTE ADENOSINE TRIPHOSPHATASE ACTIVITY IN PATIENTS WITH GASTRO-INTESTINAL CARCINOMA. (E.) Dimitrov, N. V. (Hahnemann Med. Coll. Philadelphia, Pa.) and J. Ellegaard. *New Eng J Med* 286(7):353-355, 1972.

Adenosine triphosphatase activity, expressed as micro-moles inorganic phosphate liberated per mg protein in

30 min at 37°C, is studied in patients with carcinoma of the gastrointestinal tract. Partially purified homogenates of small to medium size lymphocytes obtained from 14 patients with histologically proved carcinomas of the G.I. tract, hypopharynx(1), esophagus (4), stomach(3), gallbladder(1) and colon(5), were used. All but three patients were untreated. Twenty-two normal hospital volunteers and ten patients with various nonmalignant diseases of the G.I. tract were used as controls. The ATP-ase activity of lymphocytes from patients with cancer was  $1.42 \pm 0.18$  which was significantly ( $p < 0.001$ ) higher than that of patients with nonmalignant processes ( $0.28 \pm 0.04$ ) and that of normal controls ( $0.29 \pm 0.03$ ). No significant difference in activity was noted between lymphocytes from patients with nonmalignant G.I. lesions and those with non-malignant conditions of other organs. Addition of ouabain (0.5 mM) to the assay mixture had no effect on ATP-ase activity of either lymphocytes from normal controls or on those from patients with G.I.-tract carcinoma. Oligomycin (20  $\mu$ g/ml) decreased ATP-ase activity in all experiments. 2,4-Dinitrophenol (0.1 mM) increased activity to varying degrees in all groups. Omission of Na or K did not affect enzyme activity, whereas the addition of sodium fluoride (10 mM) or replacing magnesium chloride by calcium chloride, totally inhibited ATP-ase activity.

- 2632 TISSUE ISOANTIGENS A,B. AND H IN CARCINOMA OF THE STOMACH. (E.) Davidsohn, I. (Chicago Med. Sch., Ill.), L. Y. Ni and R. Stejskal. *Arch Path* 92(6):456-464, 1971.

Isoantigens A, B and H of human red blood cells of groups A,B and O are also present in normal epithelial cells of gastric mucosa and in arterial endothelial cells throughout the body. The effect of carcinomatous transformation on these three antigens in primary and metastatic carcinoma of the stomach was studied with the specific red cell adherence (SRCA) test, a modification of the technique of Coombs et al. Of 95 primary carcinomas, for 70 a negative SRCA reaction was found, for 5 a positive reaction and for 20 a questionable reaction. In 63 autopsies of patients with gastric carcinoma 170 metastases were found, 149 of these having a negative SRCA. Loss of demonstrable A,B and H isoantigens paralleled the degree of anaplasia. The possible use of the SRCA test in the early diagnosis and prognosis of carcinoma of the stomach was suggested.

- 2633 BCG VACCINATION AND LEUKAEMIA MORTALITY. (E.) Berkeley, J. S. (Dept. Soc. Med., U. Edinburgh, Scotland). *Health Bull* 29(3):167-169, 1971.

A study of deaths in Scotland from leukemia in persons under 15 yr is presented. Comparison of mortality rates in Glasgow, Edinburgh, Aberdeen and Dundee is associated with BCG vaccination policies in those cities. A total of 987 death certificates for the years 1939-1968 are examined and the periods



before and after BCG vaccination was established are compared. Problems in analyses of data arise from the actual classification of leukemia, the known geographical variation in leukemia mortality, and the linking of appropriate BCG records to their proper death certificate. Beginning in 1952 Glasgow initiated a program of BCG vaccination of newborns. In Edinburgh and Aberdeen, vaccination of school-leavers was started in 1953, while in Dundee the same program was begun in 1955. Analysis of Glasgow showed the annual mortality rate for leukemia in the 0-4 yr age group rose (1.81 to 4.01/100,000 population) in the two periods reviewed. Edinburgh showed an increase in the 5-9 yr age group (1.81 to 4.13/100,000 population) for the two periods studied. Aberdeen showed higher rates of mortality in both time periods for the age group 5-9 yr (4.29 to 4.25/100,000 population). No definite conclusions are cited in spite of mortality rate changes noted. In addition, no justification is found in evidence reviewed to advocate a broader policy of infant BCG vaccination.

- 2634 ENHANCEMENT OF CYTOTOXIC ACTIVITY OF IMMUNE PERITONEAL LYMPHOCYTIC CELLS AGAINST ANTIGEN-IC TUMOR CELLS AFTER *IN VITRO* CULTURE. (E.) Sudo, H. (Tokyo Biochem. Res. Inst., Japan) and Y. Hashimoto. *Gann* 62(4):275-281 (and plates LVI-LVII), 1971.

Male Donryu rats were immunized with Yoshida sarcoma cells by s.c. or i.p. injections; peritoneal fluid cells were collected from immunized and non-immunized rats. Peritoneal fluid cells were purified by washing with heat-inactivated rat serum and macrophages were removed; the resulting peritoneal fluid cells consisted of 80-95% lymphocytes. In some cases, both immune and non-immune lymphocytes were cultured for 24-72 hours with or without Yoshida sarcoma cells, after which fresh sarcoma cells were added to the cultures. Alternatively, lymphocytes which had not previously been cultured with sarcoma cells were mixed with sarcoma cells. When immune lymphocytes which had not previously been cultured with sarcoma cells were cultured with sarcoma cells, the percentage of tumor cells in the mixture dropped to 65-80% of control (controls were Yoshida sarcoma cells cultured alone) after three hours of incubation in one case, and to 30-50% of control in another case. When lymphocytes which had been cultured with or without sarcoma cells were mixed with sarcoma cells, the percentage of sarcoma cells dropped to 7-40% of control by the third hour of incubation. The evidence was that the enhancement of cytotoxic activity of immune lymphocytes after culture was due to enhanced activity of surviving effector lymphocytes, and not to increased numbers of effector lymphocytes in culture.

- 2635 SERUM ALPHA<sub>1</sub>-FETOGLOBULIN WITH GASTRIC AND PROSTATIC CARCINOMAS. (E.) Mehlman, D. J. (John Hopkins U. Sch. Med. Hosp., Baltimore, Md.), B. H. Bulkley and P. H. Wiernik. *New Eng J Med* 285 (19):1060-61, 1971.

A case history of a 77-yr-old patient with gastric and prostatic carcinomas and serum alpha<sub>1</sub>-fetoglobulin is presented. Suprapubic prostatectomy was performed for relief of prostatic enlargement. A mass in the gastric fundus was seen by radiologic examination; hepatomegaly with multiple filling defects was revealed by a liver scan. Alpha<sub>1</sub>-fetoglobulin was found in the patient's serum using a gel-diffusion immunologic technique. The patient died on the 30th hospital day; a primary well-differentiated mucous-producing adenocarcinoma of the gastric fundus along the lesser curvature was revealed at autopsy. It is suggested that the gastric or prostatic carcinoma and not an occult hepatoma produced alpha<sub>1</sub>-fetoglobulin.

- 2636 RELATION BETWEEN PLASMA-CORTISOL, PLASMA-ANDROGEN-SULPHATES, AND IMMUNE RESPONSE IN WOMEN WITH BREAST CANCER. (E.) Mackay, W. D. (Maryfield Hosp., Dundee, Scotland), M. H. Edwards, R. D. Bulbrook and D. Y. Wang. *Lancet* (7732):1001-1002, 1971.

Plasma cortisol, androgen sulfate, and the intensity of the delayed hypersensitivity reaction to tuberculin were measured in 25 untreated breast cancer patients (33-75 years, mean age 55 years) to determine whether immunologic and endocrinologic abnormalities are present in the same patient. In the cancer group 12 of 25 patients (48%) were Mantoux-positive as compared to 20 of 26 (81%) in the control group. Age-corrected results indicated that plasma dehydroepiandrosterone and androsterone sulfate levels were higher and plasma cortisol levels were lower in Mantoux-positive than in Mantoux-negative cancer patients. It is concluded that a correlation exists between endocrine and immune system functions in breast cancer patients.

- 2637 THE EFFECT OF POLYINOSINIC-POLYCYTIDYLIC ACID ON THE IMMUNE RESPONSE OF MICE TO ANTIGENICALLY DISTINCT TUMORS. (E.) Fisher, J. C. (Boston U., Sch. Med., Mass.), S. R. Cooperband and J. A. Mannick. *Cancer Res* 32(5):889-892, 1972.

NaCl suspensions of polyinosinic-polycytidylic acid (poly IC) (10 to 400 µg/day) were administered i.p. to C57BL/6J mice bearing methylcholanthrene-induced fibrosarcomas and to C3H/HeJ mice bearing polyomas, and the effects on tumor growth, humoral antibody and cellular immunity were assessed. The effect of poly IC on tumor growth was determined in the following manner: Suspensions of tumor cells were prepared and mice were challenged with 10<sup>3</sup> tumor cells in the hind leg. After appearance of visible and palpable tumors (3x3 mm), groups of ten to 12 animals were given poly IC. Tumor-bearing controls received only 0.85% saline solution. Growth was followed by measurement of the tumor bidirectionally and by calculation of tumor volumes. Poly IC caused a significant, although temporary, delay in the growth rates of both types of tumors. Most tumors eventually killed their hosts, although about 4% of mice bearing polyomas showed total tumor regres-

sion. The effect was dose related within the range of ten to 400  $\mu\text{g}$  poly IC per day. A dose of 400  $\mu\text{g}$ /day was fatal (within three to five days). Poly IC also commonly caused lymphopenia. Effect of poly IC on humoral and cellular immunity of normal mice was studied by pretreating groups of ten to 12 mice with poly IC (100  $\mu\text{g}$  i.p. on alternate days) for periods ranging from one to 28 days prior to hemolytic plaque assays. Mice were challenged with i.v. injection of 0.25% packed SRBC. Mice receiving poly IC for one to seven days demonstrated plaque-forming cell counts significantly less than controls (0.85% saline injection). Administration of poly IC from seven to 28 days (amounts that produced tumor inhibition) revealed a variable response that showed no predictable pattern. Poly IC was able to depress cellular immunity. Skin allografts exchanged between H-2-incompatible strains (C57BL/6 C3HeJ) remained viable for significantly ( $P < 0.05$ ) longer periods of time (median time to rejection of 13.3 days) than controls when poly IC was given prior to grafting and continued (100  $\mu\text{g}$  i.p. on alternate days) until day of rejection. The degree of immunosuppression was equivalent to that seen following administration of 0.1 ml ALS. For determination of the role of the immune system in the observed effects of poly IC on tumor growth, groups of ten to 12 mice were immunosuppressed with either sublethal irradiation or ALS and then challenged with  $10^3$  tumor cells. When palpable tumors appeared poly IC treatment was begun (100  $\mu\text{g}$  i.p. three times/wk.). Both tumors were inhibited despite host immunosuppression. Poly IC was not acting simply by reversing the immunosuppressive effects of ALS. It thus appeared that some mechanism other than stimulation of the immune response of the host was responsible for the effects of poly IC on malignant cells.

- 2638 CELL-MEDIATED TUMOR ALLOGRAFT IMMUNITY: *IN VITRO* TRANSFER WITH RNA. (E.) Likhite, V. (Lab. Biophysical Immunochimistry, McGill U., Quebec, Canada) and A. Sehon. *Science* 175(4018):204-205, 1972.

Results of experiments on inhibition of migration of spleen cells from Sa-1 immunized mice and transfer of this immunity to nonimmune spleen cells with RNA extracts of spleens and lymph nodes from animals rejecting Sa-1 tumors are presented. Sa-1 tumor cells were grown in the ascites form in A/J mice and injected s.c. into adult C57BL/6J mice, with a second injection being given i.p. three or four days later. Significant inhibition of migration of spleen cells from these Sa-1 immunized mice was seen when the antigen from normal A/J lymph nodes was at a concentration of 100  $\mu\text{g}/\text{ml}$  or more. No inhibition was seen when spleen cells from nonimmunized mice were used. RNA was extracted from lymph nodes and spleens of C57BL/6J mice; spleen cells from nonimmunized mice treated with RNA from nonimmunized mice showed no migration inhibition. Migration inhibition of cells treated with RNA from immunized mice was obtained, however, with A/J antigens being used. It was shown that unknown RNA extracts could be correctly identified on the basis of activity transferred. The exact chemi-

cal nature of the transfer factor and mechanism has yet to be determined.

- 2639 INTERFERON AND ANTIBODY PRODUCTION IN INBRED MICE INFECTED WITH THE RAUSCHER VIRUS. (E.) Toth, F. D. (U. Med. Sch., Debrecen, Hungary), L. Vaczi and C. Berencsi. *Acta Microbiol Acad Sci Hung* 18(1):23-27, 1971.

Antibody and interferon production and splenomegaly caused by the Rauscher leukemia virus was studied in eight-wk-old inbred Balb/c, C57BL/10Sn and DBA/1 mice. Balb/c mouse spleens were 30 to 40 times normal size within four weeks postinfection; almost all these mice died within 40 days. Splenomegaly was least severe in the C57BL/10Sn mice; this strain also showed the greatest amount of antibody production as determined by the indirect fluorescent antibody test, with DBA/1 mice producing almost as much antibody. The DBA/1 peak interferon titer was found to be five times higher than that for the other two mouse strains. It is postulated that the good immune response seen in DBA/1 mice may be due to their good interferon production.

- 2640 SYNTHESIS OF  $\alpha$ -FETOPROTEIN BY LIVER, YOLK SAC, AND GASTROINTESTINAL TRACT OF THE HUMAN CONCEPTUS. (E.) Gitlin, D. (U. Pittsburgh Sch. Med., Pa.), A. Perricelli and G. M. Gitlin. *Cancer Res* 32(5):979-982, 1972.

The synthesis of serum  $\alpha$ -fetoprotein was studied in 16 human embryos and fetuses between 4.2 and 18 wk of gestation by incubation of selected tissues in  $^{14}\text{C}$ -labeled amino acids followed by immunoelectrophoresis of the culture fluids and radioautography. As controls, fetal serum instead of tissue was incubated in culture medium with and without radiolabeled amino acids. Cultures of liver consistently yielded relatively large amounts of labeled  $\alpha$ -fetoprotein (2+ to 4+ on a scale of 0 to 4+). None of the cultures of lung, thymus, pancreas, skeletal muscle, amnion, or chorion revealed any labeled  $\alpha$ -fetoprotein. Yolk sacs obtained at 4.5 to 8.5 wk gestation actively synthesized labeled  $\alpha$ -fetoprotein (1+ to 4+). Yolk sacs obtained after 11.5 wk gestation were solid and atretic and showed much less labeling. Radioactive  $\alpha$ -fetoprotein was detected in the gastrointestinal tract of nine of the ten conceptuses so studied although the degree of labeling was very much less than that of liver cultures. Kidney cultures from at least one conceptus produced a faint  $\alpha$ -fetoprotein line on radioautography. Only one of the 14 different cultured placentas synthesized  $\alpha$ -fetoprotein.  $\alpha$ -Fetoprotein was not detected in any of the controls.

- 2641 LYMPHOCYTE BLASTOGENIC RESPONSES TO CULTURED ALLOGENEIC TUMOR CELLS *IN VITRO*. (E.) Anderson, R. J. (U. Texas, M. D. Anderson Hosp. Tumor Inst., Houston), C. M. McBride and E. M. Hersh. *Cancer Res* 32(5):988-992, 1972.



Experiments involving blastogenic responses of normal lymphocytes to allogeneic, cultured human tumor cell lines were performed to determine ideal *in vitro* conditions necessary for studying these interactions. Fourteen human tumor cell lines were used; cell suspensions were irradiated with 4,000 rads for use as stimulators of lymphocyte blastogenesis. All 14 cell lines produced significant blastogenic responses, with most stimulation occurring when  $5 \times 10^4$  irradiated tumor cells stimulated  $10^6$  lymphocytes. The median of the maximal response was 3,700 cpm, with a range of 1,260 to 28,083; above a median dose of  $5 \times 10^4$  cells blastogenic responses were usually reduced or absent. Tumors stimulated less blastogenesis than that induced by mitogens, antigens, lymphocytes or lymphoblasts, with lymphoblasts inducing more blastogenesis than the normal small lymphocytes. An inhibitor of lymphocyte blastogenesis was found in the supernatant of mitomycin-treated or irradiated tumor cell cultures; it was nondialyzable and appeared 30 min after the cells were placed in culture. The inhibitor was found when high *in vitro* tumor cell doses were used. It is postulated that formation of a large amount of inhibitor might be helpful for blocking *in vivo* tumor growth.

- 2642 SKIN CANCER AND IMMUNOSUPPRESSION. (E.) Walder, B. K. (Prince Henry Hosp., Little Bay, N.S.W., Australia), M. R. Robertson and D. Jeremy. *Lancet* (7737):1282-1283, 1971.

Kidney transplant patients treated with immunosuppressive drugs for up to six years after transplantation were examined for skin lesions. Of 51 patients studied seven (14%) had malignant skin cancers. Most of the cancers were found on the exposed areas of the hands, arms and neck. Numerous hyperkeratoses had been present in two patients; multiple squamous cell carcinomas developed in these patients. Keratoacanthoma developed in three patients and tended to recur. The finding of 19 skin cancers in 14% of the patients suggests that immunosuppressive treatment may increase chances of skin cancer. It is further suggested that an important initiating factor in skin cancer development may be high solar exposure.

- 2643 IMPENETRABILITY OF THE MOUSE PLACENTA TO MATERNAL LEUKAEMIA CELLS. (E.) Loewenstein, D. (Tufts U. Sch. Med., Boston, Mass), W. L. Hughes, K. G. Hofer and M. M. Ketchel. *Nature* 231(5302):389-391, 1971.

A virulent strain of leukemia cells is utilized to test penetration of the placental barrier. In a time-vs-number-of-cells series, 47 pregnant DBA/2 mice received injections of a virulent murine lymphocytic leukemia. Between two and 17 days after inoculation the mice were sacrificed and a total of 183 fetal mice recovered. Precautions were taken to prevent leukemia cells from contaminating the surface of the fetuses. An inoculation was prepared from the whole fetal specimens

(homogenate) and injected into adult female DBA/2 mice. These secondary test mice were then observed for a six-wk period for signs of leukemia. A control normal fetal series was prepared, using liver cells and  $^{125}\text{I}$ -labeled leukemia cells. Results showed that all leukemia-cell-injected pregnant mice did in fact develop leukemia. None of the 204 recipients of tissue from 183 fetuses died from leukemia, indicating that leukemia cells were not transferred from mother to fetus. Additional tests using hyaluronidase, which increases placental permeability, were carried out. Results from this phase of testing indicated that passage of leukemia cells in hyaluronidase-treated pregnant mice is not a generally occurring phenomenon.

- 2644 LOCALIZATION OF COMPLEMENT-FIXING ANTIGENS IN CELLS: EPSTEIN-BARR VIRUS-INDUCED MEMBRANE AND INTERIOR CELL ANTIGENS. (E.) Hollinshead, A. (George Washington U. Med. Ctr., Washington, D.C.), O'B. Lee and T. C. Alford. *J Gen Virol* 13(3):441-447, 1971.

All cell membrane fractions, soluble cell-membrane components and cell interiors of lymphoblastoid cell line IM<sub>1</sub>, leukemic lymphoid cell line RPMI-4265, and Burkitt lymphoma cell line P<sub>3</sub>, were tested for complement-fixation activity and histocompatibility antigen (HL-A). Complement-fixation activity was seen between IM<sub>1</sub> cell membranes and three sera from Burkitt's lymphoma patients, whereas little fixation was seen between P<sub>3</sub> cell membranes and these sera. Complement-fixation was seen between IM and RPMI-4265 cell interiors and the Burkitt and infectious mononucleosis sera. No fixation was observed when sera from seven American lymphoma patients or guinea-pig hyperimmune sera against types 1 and 2 herpes simplex virus were used. Complement-fixation activity was also detected in a high-molecular-weight soluble RPMI-4265 membrane antigen purified on a Sephadex G-200 column and in purified lymphoma cell interior sonicates. The complement-fixing reactive component and HL-A antigens were separated by disc gel electrophoresis.

- 2645 T OR B LYMPHOCYTES IN CHRONIC LYMPHOCYTIC LEUKAEMIA. (E.) Moore, G. E. (Roswell Park Memorial Inst., Buffalo, New York) and J. Minowada. *Lancet* (7740):38-39, 1972.

The establishment of a cell line with many unusual characteristics suggesting a T lymphocyte from an adult with acute lymphatic leukemia is reported. This cell line: 1) has many small mature forms; 2) contains very sticky cells which do not clump; 3) has cells which do not produce immunoglobulin; 4) shows no apparent membrane receptor sites for immunoglobulin and complement; 5) has a majority of cells forming rosettes with sheep red blood cells; and 6) has cells which multiply slowly. This abnormal cell line fortunately adapted to the culture conditions used and retained these indirect T-cell characteristics.

- 2646 LYMPHOCYTE-MEDIATED CYTOTOXICITY IN VITRO: EFFECT OF ENHANCING ANTISERA. (E.) Klein, W. J., Jr. (Duke U. Med. Ctr., Durham, N.C.). *J Exp Med* 134(5):1238-1252, 1971.

An *in vitro* model for studying lymphocyte-mediated cytotoxic effects on tumor cells is described. This model was used for studying the reaction of immune lymphocytes against BP8 ascites tumor cells and for determining the effect of antisera with known enhancing activity *in vivo* on these *in vitro* reactions. The results indicated: 1) no cytotoxicity was produced by normal lymph node cells (LNC) or LNC obtained after immunization with Freund's adjuvant; 2) active cytotoxicity to tumor cells was produced by specifically immune LNC sensitized *in vivo*; 3) the lymph node cells showed lymphocytotoxic activity five to seven days after immunization; and 4) the lymphocyte:target cell ratio found to yield the best results was 10-24:1. S.C. immunization appeared to have been a more potent stimulus to cellular immunity in lymph nodes than i.p. immunization. The results obtained supported the hypothesis of a mechanism of antibody-mediated immunosuppression by a central mechanism of enhancement. When immunized LNC were exposed to washed, antibody-treated tumor cells, no cytotoxic activity was noted and no effect was noted upon incubation with antibody alone. It is concluded that antigen-antibody complexes have a direct immunosuppressive effect on the lymphocyte.

- 2647 HOST-GENE CONTROL OF C-TYPE RNA TUMOR VIRUS: INHERITANCE OF THE GROUP-SPECIFIC ANTIGEN OF MURINE LEUKEMIA VIRUS. (E.) Taylor, B. A. (Jackson Lab., Bar Harbor, Me.), H. Meier and D. D. Myers. *Proc Nat Acad Sci USA* 68(12):3190-3194, 1971.

The inheritance of the group-specific antigen of murine leukemia virus (MuLV) and the expression of infectious MuLV were studied in F<sub>1</sub> and F<sub>2</sub> hybrids and in F<sub>1</sub> x parental backcrosses of high-leukemia AKR/J and low-leukemia C57L mice and in partially inbred lines (AKXL) derived from the above F<sub>2</sub> hybrids. Group-specific antigen present in the spleen was detected by the complement-fixation test. All F<sub>1</sub> and AKR-backcross mice were found to be antigen-positive; it was concluded that gene(s) premissive for the expression of the antigen were dominant or semi-dominant to their nonpermissive alleles. Antigen-negative mice appeared among the F<sub>2</sub> and C57L-backcross populations in proportions suggesting the presence of simultaneous homozygosity of recessive alleles to two independently inherited autosomal genes. Plaque formation studies using SWR/J, BALB/cJ and C57J/J tissue cultures infected with spleen preparations indicated that most, if not all, backcross and F<sub>2</sub> mice had complete, replicating virus. Antigen determinations in recombinant inbred lines were consistent with a single gene dominant model for determining antigen presence in AKXL cells. A very good, although incomplete, correlation was found between the presence of viral antigen and complete virus. The results were interpreted to mean that the antigen was a necessary, but not the sole, determinant for complete virus production. The presence of two

dominant genes was required for complete virus production in AKR mice. Attempts to map these loci by linkage testing were unsuccessful.

- 2648 INHIBITORY EFFECTS OF ANTICELLULAR ANTIBODIES ON COLONY FORMATION OF MOUSE LEUKEMIA L5178YR CELLS IN SOFT AGAR. (E.) Yang, T. J. (Dept. Microbiol., McGill U., Montreal, Quebec, Canada) and S. I. Vas. *Canad J Microbiol* 18(1):83-86, 1972.

Heat-inactivated rabbit antiserum in the absence of complement was used to inhibit colony formation in mouse leukemia L5178YR cells in soft agar. The cell-containing agar layer was overlaid with antisera dilutions to prevent the agglutination of the cells at increased concentrations of antisera and ensure even diffusion of the antiserum into the cells. After four subpassages the resistant clones still showed no marked increase in resistance to the same antiserum. These results indicate that cell agglutination by antiserum is not always the essential cause of growth inhibition. It is postulated that membrane alterations may be responsible for such inhibition; some indirect mechanism may have been triggered on the cell surface by the antigen-antibody reaction.

- 2649 POST-BIOPSY BREAST CARCINOMA: A NATURAL EXPERIMENT IN CANCER IMMUNOLOGY. (E.) Black, M. M. (New York Med. Coll., N.Y.), S. J. Cutler and T. H. C. Barclay. *Cancer* 29(1):61-65, 1971.

Case studies of patients from the Cancer Clinic of the Saskatchewan Cancer Commission with *in situ* breast cancer who subsequently developed invasive cancer, and a reevaluation of reported "benign" breast biopsies, are presented and discussed. Breast cancers arising in patients with a history of precancerous mastopathy were shown to have had more favorable stage and survival characteristics than those patients with breast cancers preceded by normotypic lesions, unselected breast cancers and prior invasive cancers. The results indicated a cross-reacting immunologic response in patients with *in situ* breast cancer.

- 2650 COMMON ANTIGEN IN MENINGIOMA-DERIVED CELL CULTURES. (E.) Catalano, L. W., Jr. (Coll. Phys. Surg., Columbia U., New York, N.Y.), D. H. Harter and K. C. Hsu. *Science* 175(4018):180-182, 1972.

An immunologic study using fluorescence techniques to demonstrate a common antigen in meningioma-derived cell cultures prepared from central nervous system tumors is reported. Antibody in serum of patients with intracranial meningiomas appeared to be specific for antigens in meningioma tissue, as shown by immunofluorescence assays with cell cultures and tumor imprints prepared from human meningiomas. There was some cross-reactivity noted with neoplastic tissue of glial



- origin. The presence of immunofluorescence antibody in human sera cannot be considered diagnostic of meningioma or other brain tumors at this time. It may result from experience with a relatively common antigen which is preferentially localized in neoplastic cells but may be completely unrelated to the oncogenic process.
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- 2655 AUGMENTED IMMUNOGENICITY OF TUMOR CELL HOMOGENATES INFECTED WITH INFLUENZA VIRUS. (E.) Boone, C. W. (Natl. Cancer Inst., Bethesda, Md.) and K. Blackman. *Cancer Res* 32(5):1018-1022, 1972.
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- 2658 THE STUDY OF ORGAN-SPECIFIC ANTIGENS OF THE MUCOUS MEMBRANE OF THE STOMACH, TUMORS AND THEIR METASTASES. (Rus.) Korolj, T. M. (P. A. Herzen Res. Inst. Oncology, Moscow, USSR) and B. E. Chechik. *Vop Onkol* 17(11):17-19, 1971.
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- 2678 HL-A PHENOTYPES IN HODGKIN'S DISEASE: PRELIMINARY REPORT. (E.) Kissmeyer-Nielsen, F. (U. Hosp., Aarhus, Denmark), K. B. Jensen, G. B. Ferrara, K. E. Kjerbye and A. Svejgaard. *Transplantation Proc* 3(3):1287-1289, 1971.
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- 2681 STUDIES ON THE ETIOLOGY OF TROPHOBLASTIC TUMORS. II. THE INCIDENCE OF SEX CHROMATIN IN TROPHOBLASTIC TUMORS. (Jap.) Nishio, Y. (Gifu U. Sch. Med., Japan). *Acta Sch Med Univ Gifu* 18(4):439-448, 1970.
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- 2703 LOCALIZATION OF AN  $^{125}\text{I}$ -LABELED RAT TRANSPLANTATION ANTIBODY IN TUMORS CARRYING THE CORRESPONDING ANTIGEN. (E.) Izzo, M. J. (U.

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See also:

- \* (Rev): 2202, 2204, 2208, 2211, 2220, 2233, 2245, 2254, 2260, 2262, 2272, 2290, 2294, 2295, 2296, 2297
- \* (Chem): 2308, 2316, 2326, 2336, 2367
- \* (Viral): 2500, 2515, 2516, 2526, 2535, 2538, 2540, 2546, 2551, 2576, 2587, 2601
- \* (Path): 2732



- 2716 STUDIES OF LDH ACTIVITY CONCERNING MALIGNANT TRANSFORMATION FROM CHRONIC SINUSITIS. (E.) Fujisaki, S. (Osaka U. Med. Sch., Japan), S. Sakai and M. Ishida. *Acta Otolaryng* 73:61-63, 1972.

LDH activity was determined in homogenates of surgical specimens of paranasal mucosa from 26 patients with maxillary cancer, 69 patients with chronic sinusitis, 10 patients with nasal polyps and five postirradiation patients with maxillary cancer. LDH activity in patients with untreated maxillary cancer was at least twice as high ( $2910 \pm 660$  U/mgN) as that in any of the other patients. Electrophoretic analysis yielded five isozyme patterns (LDH<sub>1</sub> to LDH<sub>5</sub>). Chronic sinusitis and maxillary cancer patients showed high activities for fractions LDH<sub>3</sub>, LDH<sub>4</sub> and LDH<sub>5</sub>. LDH<sub>4</sub> and LDH<sub>5</sub> were the predominant forms in maxillary cancer and were designated "Cancer type"; LDH<sub>3</sub> prevailed in chronic sinusitis and was designated "Inflammation type". A designation of ten types of the LDH isozyme pattern, covering "Inflammation" and "Cancer types" was proposed. The histologically proliferative type in chronic sinusitis and LDH activity of mucosae with squamous metaplasia both tended to resemble the "Cancer type" in their isozyme patterns.

- 2717 MORPHOLOGIC AND BIOLOGIC CORRELATION OF HYPERPLASTIC AND NEOPLASTIC HEPATIC LESIONS OCCURRING "SPONTANEOUSLY" IN C<sub>3</sub>H x Y HYBRID MICE. (E.) Reuber, M. D. (Nat'l. Cancer Inst., Bethesda, Md.). *Brit J Cancer* 25(3):538-543, 1971.

Wedges of tissue from hyperplastic areas and hyperplastic nodules, and from carcinomatous areas, of spontaneous lesions developed in livers of C<sub>3</sub>H x Y hybrid mice were implanted s.c. in the same individuals (autologous transplantation) or in different individuals of the same strain (isologous transplantation). Autologous transplants of areas of hyperplasia and of nodules of hyperplasia failed to grow in 23 and 14 mice, resp. Autologous transplants of large hepatocellular carcinomas were successful in five of five attempts. Isologous transplants of areas of hyperplasia, nodules of hyperplasia, small hepatocellular carcinomas, and large hepatocellular carcinomas, survived in 0/53, 0/42, 2/3 and 20/22 cases, resp. Transplanted carcinomas grew and killed their autologous or isologous hosts.

- 2718 FUNCTIONAL CHARACTERISTICS OF THYROID CARCINOGENESIS IN RATS: A CHROMATOGRAPHIC STUDY. (Ger.) Christov, K. (Oncol Res. Inst., Chem.-Tech. Sch., Sofia, Bulgaria) and M. Kristeva. *Arch Geschwulstforsch* 37(3):257-265, 1971.

Changes induced in the I-131 metabolism of thyroid glands of rats by methylthiouracil administration for periods of 120 and 450 days were investigated using paper chromatography and autoradiography to determine if thyroid tumor cells could metabolize iodine up to the level of triiodotyronine and thy-

roxine. The thyroid of control rats contained 9.1% of the isotope 24 hours following the administration of 100  $\mu$ C I-131. Of the iodine-containing components, diiodotyronine contained 38.3% and monoiodotyronine 33.2% of the isotope. The iodine content of thyroxine was about three times that of triiodotyronine. The quantity of I-131 stored in the thyroid of rats treated until the test day with methylthiouracil was only one tenth of that stored in the thyroid of control rats. Chromatography disclosed only inorganic I-131. A two-week discontinuation of methylthiouracil administration resulted in a resumption of normal hormonal synthesis by the thyroid epithelium except for triiodotyronine, which was found to be three times higher than in untreated control rats. In cells of two out of six thyroid tumors, a small amount of mono- and diiodotyronine was found; in the remaining 4 tumors no organic I-131 was present. Thyroid cells lose their ability to synthesize thyroid hormones as a result of tumorigenesis.

- 2719 THE PROLIFERATION OF CAPILLARY ENDOTHELIAL CELLS. (E.) Tannock, I. F. (U. Texas, M. D. Anderson Hosp. Tumor Inst., Houston) and S. Hayashi. *Cancer Res* 32(1):77-82, 1972.

Thymidine autoradiography was used to investigate the proliferation of endothelial cells in mice in a variety of normal tissues, in tissues damaged by irradiation and in the callus formed after fracture of the femur. Proliferation of endothelial cells in unstimulated C<sub>3</sub>H/He mouse tissue gave a thymidine-labeling index for endothelial cells in the range of 0 to 2.4%. The labeling index for capillary endothelial cells at intervals after irradiation of a single dose of 2000 or 4000 rads showed no increase in irradiated muscle, skin or bone, at three weeks after 2000 rads, or up to two weeks following 4000 rads. Proliferation of endothelial cells in regenerating callus after fracture of the femur showed a mean labeling index of nine percent on the fifth day with a decrease to zero on the 16th day. The double-labeling experiment showed the estimated duration of DNA synthesis,  $7 \pm 2$  hr, to be within the range found for most mouse tissues. The results of the repeated labeling experiments gave a turnover time of  $80 \pm 25$  hr on the sixth day following the fracture. The turnover time was approximately 50 hr at three days after the injury. The results suggest the existence of an angiogenesis factor (or some agent which depresses normal inhibitors) that is activated by injury.

- 2720 THE OCCURRENCE OF BACILLUS VAGINALIS DÖDERLEIN AND CYTOLYSIS IN DYSPLASIA, CARCINOMA IN SITU, AND INVASIVE CARCINOMA OF THE UTERINE CERVIX. (E.) Nasiell, K. (Inst. Path., Sabbatsberg Hos., Sweden), J. Dudkiewicz, M. Nasiell, A. Hjerpe and C. Silfverswärd. *Acta Cytol* 16(1):21-25, 1972.

A total of 440 cases of cervical neoplastic condition were divided into four equal groups: 1) cases with a

histologic confirmation of a diagnosis of invasive carcinoma; 2) cases with a histologic diagnosis of moderate to severe dysplasia; 3) cases with a histologic diagnosis of carcinoma in situ and 4) cases with negative cytology. The patients in each group ranged in age from 26 to 45 years old. *Bacillus vaginalis* Döderlein (BVD) was assayed in each case using the latest positive smear prior to biopsy. The microbiologic findings were classified into four groups: 1) distinct forms of BVD with or without cytolysis; 2) mixed flora; 3) other microbiologic findings; and 4) no visible microorganisms. The highest incidence of BVD was seen in the control group and the lowest in the invasive carcinoma series. Out of 13 cases of invasive carcinoma with BVD, four (30%) (i.e., 4% of the total invasive series) showed unquestionable cytolysis. The highest incidence of cytolysis was in the control group, and a lower and similar frequency was seen in the dysplasia and carcinoma in situ groups.

- 2721      EPITHELIAL ALTERATIONS IN THE EXTRALOBULAR DUCTS OF BREASTS WITH LOBULAR CARCINOMA. (E.) Fechner, R. E. (Baylor Coll. Med., Houston, Tex.). *Arch Path* 93(2):164-171, 1972.

Epithelial alterations in the extralobular ducts of 45 breasts with lobular carcinoma are studied. The breasts had been removed by simple or radical mastectomy. Lobular carcinoma in situ (CIS) was present in 55% of the cases; the remaining 45% were diagnosed as demonstrating infiltrating lobular carcinoma. The presence or absence of interlobular duct (lactiferous duct) involvement was tabulated. Thirty-four of the 45 breasts with lobular carcinoma had alterations in the interlobular ducts. Intramural hyperplasia was the pattern found most useful as a clue that the lobular carcinoma might be present elsewhere in the breast. Cytologically, the cells of the interlobular ducts, lobular CIS and infiltrating lobular carcinoma were identical in any given case. Histologically, two major patterns were seen: 1) intramural hyperplastic pattern, and 2) solid pattern. Two other patterns noted were a cribriform appearance and a fine papillary pattern which seemed to be only variations of the solid pattern. It is suggested that recognition of any of these interlobular duct changes should alert the examiner to the possibility of lobular carcinoma elsewhere in the breast.

- 2722      GLYCOLYTIC ENZYME ACTIVITY IN BLADDER TUMORS. (E.) Carr, A. J. (Dept. Path., U. Aberdeen, Scotland) and J. H. Steyn. *South Afr Med J* 46(3):48-50, 1972.

The activity of  $\beta$ -glucuronidase and  $\beta$ -N-acetyl glucosaminidase was studied in normal human bladder tissue, benign bladder papilloma and in bladder carcinoma. The enzyme activity was measured spectrophotometrically and a comparison was made of the activity of the different grades of tumor. The enzyme activity values for normal bladder mucosa are low. The values for the benign papilloma are much

higher than for normal tissue, rising higher with the change to a well differentiated malignant tumor. However, as the degree of malignancy increases, the values drop down to almost the same level as those of the benign papilloma for the anaplastic tumors. Therefore, it is not possible to predict on the basis of enzyme activity how the bladder carcinoma would behave clinically.

- 2723      TISSUE AND CELL PATHOLOGY OF UTERINE CERVIX DYSPLASIAS AND CARCINOMA *IN SITU*. (E.) Nieburgs, H. E. (Mount Sinai Sch. Med., New York, N.Y.). *Acta Cytol* 15(6):513-532, 1971.

- 2724      OXYGEN SUPPLY AND STABILITY OF CHROMOSOMES IN MOUSE EMBRYO CELLS *IN VITRO*. (E.) Parshad, R. (Natl. Cancer Inst., Bethesda, Md.) and K. K. Sanford. *J Nat Cancer Inst* 47(5):1033-1036, 1971.

- 2725      INDUCED DIFFERENTIATION OF A NEUROBLASTOMA. (E.) Schubert, D. (Inst. Pasteur, Paris, France), S. Humphreys, F. De Vitry and F. Jacob. *Develop Biol* 25(4):514-546, 1971.

- 2726      EXPERIMENTAL STUDIES OF VAGINAL SECRETION HYALURONIDASE VALUES IN PATIENTS WITH NEOPLASTIC AND NON-NEOPLASTIC CERVICAL LESIONS. (It.) Panazzolo, A. (Inst. Oncol. Turin, Italy), P. Cacciari, S. Scuro, S. Taddei and S. Masaracchia. *Arch Sci Med* 128(2):63-75, 1971.

- 2727      GROWTH AND MALIGNANCY OF OVARIAN TUMOURS IN PREGNANCY. (E.) Beischer, N. A. (Dept. Obst. Gyn., U. Melbourne, Australia), B. W. Buttery, D. W. Fortune and C. A. J. Macafee. *Aust New Zeal J Obstet Gynaec* 11(4):208-220, 1971.

- 2728      MALIGNANT CHANGE IN THE EPITHELIUM LINING ODONTOGENIC CYSTS. (E.) Browne, R. M. (Dept. Oral Path., U. Birmingham, England) and N. G. Gough. *Cancer* 29(5):1199-1207, 1972.

- 2729      COMPARATIVE STUDY OF THE CLINICAL PICTURE AND HISTOPATHOLOGIC STRUCTURE OF ORAL LEUKOPLAKIA. (E.) Banoczy, J. (Inst. Oral Maxillo-facial Surg., Budapest, Hungary) and A. Csiba. *Cancer* 29(5):1230-1234, 1972.

- 2730      MULTIPLE MYELOMA: CHROMOSOMAL ABNORMALITIES IN MULTIPLE MYELOMA. (E.) Ranjini, R. (Topeka, Kan.). *J Kansas Med Soc* 72(11):435-437, 1971.



- 2731 ISOLATION AND CHEMICAL CHARACTERIZATION OF CELL SURFACE SIALOGLYCOPEPTIDE FRACTIONS DURING PROGRESSION OF RAT ASCITES HEPATOMA AS-30D. (E.) Smith, D. F. (U. Texas Grad. Sch. Biomed. Sci., Houston) and E. F. Walborg, Jr. *Cancer Res* 32(3):543-549, 1972.
- 2732 IMMUNOLOGICAL AND CYTOGENETIC PROPERTIES OF DEVELOPING THYROID TUMORS IN THE RAT. (E.) Al Saadi, A. (William Beaumont Hosp., Royal Oak, Mich.) and G. J. Mizejewski. *Cancer Res* 32(3):501-505, 1972.
- 2733 WORK AND WATER INTAKE AND THE WATER NEED OF RATS DURING GROWTH OF A TUMOR. (E.) Morrison, S. D. (Natl. Cancer Inst., Bethesda, Md.). *Physiology Behavior* 8(1):5-10, 1972.
- 2734 THE MITOTIC VALUES FOR THE EPITHELIUM IN ORAL KERATOSES AND LICHEN PLANUS. (E.) El-Labban, N. (Dept. Path., U. London, England), R. B. Lucas and I. R. H. Kramer. *Brit J Cancer* 25(3):411-416, 1971.
- 2735 LOCATION OF AMINO ACID AND CARBOHYDRATE TRANSPORT SITES IN THE SURFACE MEMBRANE OF NORMAL AND TRANSFORMED MAMMALIAN CELLS. (E.) Inbar, M. (Weizmann Inst. Sci., Rehovot, Israel), H. Ben-Bassat and L. Sachs. *J Membrane Biol* 6(3):195-209, 1971.
- 2736 PRECANCEROUS CONDITIONS OF THE DIGESTIVE TRACT. (Ger.) Schyra, B. (Reg. Hosp. Polyclin., Bernburg, Germany) and T. Becker. *Beitr Krebsforsch Monographs* 10:1-196, 1971.
- 2737 PRECANCEROUS CONDITIONS OF THE SCALP. (Fr.) Tuca Barcelo, L. (No affiliation). *J Franc Otorhinolaryng* 20(9):1027-1028, 1971.
- 2738 PRECANCEROUS CONDITIONS OF THE INFERIOR LIP VERMILION BORDER. PREVENTIVE VERMILIONECTOMY. (Fr.) Marchac, D. (St. Louis Hosp., Paris, France) and C. Dufourmentel. *J Franc Otorhinolaryng* 20(9):1029-1032, 1971.
- 2739 PRECANCEROUS CONDITIONS OF THE ESOPHAGUS. (Fr.) Mounier-Kuhn, P. (No affiliation), J. Gaillard, J. P. Haguenauer and Ph. A. Bernard. *J Franc Otorhinolaryng* 20(7):1079-1083, 1971.
- 2740 EXPERIENCE FROM CYTOLOGIC PROGNOSIS OF CARCINOMA *IN SITU*. (Ger.) Hartmann, G. (Women's Clin. U. Heidelberg, Germany), H. H. Rummel and G. Bräunig. *Zbl Gynaek* 94(3):78-86, 1972.
- 2741 VAGINAL CERVIX CARCINOMA *IN SITU* (INCREASED ATYPICAL SQUAMOUS EPITHELIUM, H III) AS A SPECIFIC STAGE IN THE CANCERIZATION PROCESS. (Ger.) Buchmann, E. (Friedrichshain City Hosp., Berlin, Germany), P. Kaiser and L. Moltz. *Zbl Gynaek* 94(3):87-93, 1972.
- 2742 DEVELOPMENT OF PLANOEPITHELIAL CARCINOMA IN LONG-STANDING LARYNGEAL SCLEROMA. (Pol.) Klonowski, S. (Otolaryngol Clin., Lublin, Poland). *Otolaryng Pol* 25(4):441-443, 1971.
- 2743 ON KINETICS OF TUMOUR GROWTH. (Uk.) Kazmin, S. D. (Sci. Res. Inst. Exp. Clin. Oncol., Acad. Sci. Ukr. SSR, Kiev). *Dop Akad Nauk* (12):1121-1124, 1971.
- 2744 CANCERS, ASSOCIATED WITH ULCERATIVE HEMORRHAGIC RECTOCOLITIS AND OTHER INFLAMMATORY ULCERATIVE AND HEMORRHAGIC DISORDERS OF THE LARGE INTESTINE. (Fr.) Saegesser, F. (Surg. Serv. U. Lausanne, Switzerland), V. Phillips, G. Chapuis and C. Rausis. *Praxis* 61(7):200-205, 1972.
- 2745 RESPIRATORY ORGAN DISEASES, PRECEEDING BRONCHOPULMONARY CANCER. (Rus.) Ivankhno, G. I. (Kiev Sci. Res. Inst. Exp. Clin. Oncol., USSR). *Vrach Delo* 1:67-69, 1972.
- 2746 GASTRIC CARCINOSARCOMA: CASE STUDY AND POSSIBLE HISTOGENETIC INTERPRETATIONS. (It.) Tomasino, R. M. (Inst. Anat. Path. Hist., U. Palermo, Italy). *Arch Ital Anat Istol Patol* 43(5/6):364-385, 1969.
- See also:  
 \* (Rev): 2206, 2284, 2344  
 \* (Chem): 2360, 2425, 2446  
 \* (Immun): 2636

- h 2747 INTRAEPITHELIAL CARCINOMA OF THE CERVIX  
c UTERI IN WOMEN AGED UNDER 35 YEARS. (E.)  
n Davies, S. W. (Dept. Path., U. Exeter, England) and  
l R. M. Kelly. *Brit Med J* 4(5786):525-526, 1971.

r  
j A total of 45,525 cervical smears from women from  
I different age groups, primarily those with a high  
j cancer risk, were examined. Among women aged 25 to  
f 34 yr the incidence of intraepithelial carcinoma  
: was 0.67% and among those aged 35 to 44 yr it was  
: 0.75%, or a ratio of 1:1.12 between the two groups.  
: The overall rate of intraepithelial carcinoma in  
i women under 35 yr was 0.55% compared with an overall  
rate of 0.59% in women over 35 yr. In the interests  
of preventive medicine, it is suggested that prac-  
titioners should be encouraged to take cervical  
smears from younger women, especially those under  
35 yr, despite the prevailing practice of concentra-  
ting on women over 35.

- 2748 INCIDENCE RATES FOR MICROSCOPICALLY DIAG-  
NOSED CANCER IN THE SINGAPORE POPULATION  
1960-1964. (E.) Muir, C. S. (Int. Agency Res.  
Cancer, Lyon, France), K. Shanmugaratnam and K. K.  
Tan. *Singapore Med J* 12(6):323-332, 1971.

The incidence rates for microscopically diagnosed cancer in the population of Singapore were derived from Cancer Registry records and related to total population census data. Case reports were drawn from 6,624 histologically confirmed cancers seen during the period 1960-1964. A considerably greater number of cases occurred in males, reflecting the greater number of males in the over-all population. The five most frequently occurring types of cancer were: nasopharyngeal, cervical, gastric, lung, and liver. These five cancer types were related to each of four ethnic groups (Chinese, Malays, Indians, and Pakistanis) in order of frequency for that specific group, with the idea that racial group differences might be useful in elucidating etiology.

- 2749 CANCER MORTALITY IN NEW ZEALAND: 3. BREAST  
AND GENITAL ORGANS. (E.) Donovan, J. W.  
(U. Sydney, Australia). *N Z Med J* 72(462):318-322,  
1970.

The trends in mortality from cancers of the breast and genital organs in New Zealand are discussed and compared with those of specific races and levels in other countries. A review of clinical and autopsy diagnoses over a 40-year period shows that in New Zealand breast cancer mortality has not changed significantly since 1931, whereas there is a continuous decline in mortality from cancer of the cervix. The changes in diagnostic patterns and the introduction of massive screening programs have had little effect on the overall statistical incidence of these types of cancers. However, the decrease in mortality from cancer of the prostate gland is considered to be a direct reflection of improved techniques in diagnosis.

- 2750 MORTALITY FROM CARCINOMA OF THE UTERUS:  
AN INTERNATIONAL COHORT STUDY. (E.)

Adelstein, A. M. (Office Population Censuses Surveys, London, England), G. B. Hill and L. Maung. *Erit J Prev Soc Med* 25(4):186-191, 1971.

Trends in mortality from cancer of the uterus in 20 different countries are reviewed. Data for successive age groups are analyzed by cohorts, and show that cancer of the uterus has been steadily declining in successive generations of women with the exception of women born between 1911 and 1924 who reside in England, Wales, Scotland, the Scandinavian countries, New Zealand and Chile. It is suggested that this pattern, taken in conjunction with the other evidence acquired from epidemiologic studies, is considered to be related to war-time disturbances of customary sexual relationships and is best explained by an infective cause of the cancer.

- 2751 ADENOCARCINOMA OF THE NASAL CAVITY AND  
SINUSES IN ENGLAND AND WALES. (E.)

Acheson, E. D. (Dept. Comm. Med., U. Southampton, England), R. K. Cowdell and E. Rang. *Britt J Industr Med* 29:21-30, 1972.

A survey of the frequency of nasoadenocarcinoma among furniture workers, particularly woodworkers, in England and Wales is described. Data for 107 patients were acquired from cancer registries; 110 patients with nasal carcinoma of a histologic type other than adenocarcinoma were used as controls. Information is categorized according to occupation and the distribution is compared to the total population of England and Wales. Of the 107 survey patients, 80 were males and 27 were females; the control group consisted of 85 males and 25 females. This study provides additional evidence of the already recognized relationship existing between work in the furniture industry and the development of nasal adenocarcinoma. In Britain, nasal adenocarcinoma in the furniture-making industry is now a prescribed disease and the study confirms that the risk of this disease exists throughout the British furniture industry and is not limited to a specific region.

- 2752 CARCINOMA OF THE BLADDER IN THE COAST  
PROVINCE OF KENYA. (E.) Anjarwalla,  
K. A. (Coast Gen. Hosp., Mombasa, Kenya). *East Afr Med J* 48(9):502-509, 1971.

This study reviews the incidence of carcinoma of the bladder in 38 patients treated at the Coast Province General Hospital in Mombasa. The average age of the test group was 42.5 yr with maximum incidence of cancer occurring in the 50-59 year age group. A significantly high frequency of bladder cancer was found to exist in patients (90% of cases) residing in regions heavily infected by urinary bilharziasis. Analysis showed 32 patients (84%) were in poor physical condition from pain, hematuria, emaciation and anemia. Thirty-three pa-



tients (86%) had a palpable mass in the suprapubic region at first clinical examination. Radiologic examination indicated a high frequency of bladder calcification and abnormal kidneys. In 28 kidneys visualized, 60% showed varying degrees of hydronephrosis and 38% showed no kidney function at all. All patients showed metastases with 24 cases occurring to "perivesicals" and 13 with metastases to the pelvis or adjoining organs.

- 2753 CANCER OF THE ESOPHAGUS IN THE NEAR EAST. (E.) Atiyeh, M. N. (Div. Gastroenterol., American U. Beirut, Lebanon), S. M. Uthman and M. H. Shammaa. *Lib Med J* 24(3):273-277, 1971.

Ninety-three cases of carcinoma of the esophagus seen at the American University Hospital in Beirut over the last 15 years (1955-1969) are reviewed. The mean age of patients was 55 years, and the male to female ratio was three to one. Squamous cell carcinoma (60 patients) was the predominant histopathologic diagnosis. Dysphagia (94.6%) was the major presenting complaint, and two to six months (53.7%) was the most common interval of duration of symptoms. The most striking finding in this study was that more than 50% of the patients were Saudi Arabians, although the number of Saudi admissions had never exceeded two per cent of total hospital admissions. The study supports the notion that the incidence of esophageal cancer is higher in areas where irritants such as alcohol, hot tea, spices or nitrosamine are highly consumed.

- 2754 MORTALITY OF NEWSPAPER WORKERS FROM LUNG CANCER AND BRONCHITIS 1952-66. (E.) Moss, E. (Dept. of Occupational Health, Univ. of Manchester, Manchester, England) and G. R. C. Atherley. *Brit J Industr Med* 29(1):1-14, 1972.

The mortality experience of 3,485 men who worked full-time in the newspaper printing industry in London and Manchester and died in the period 1952-66 has been analysed for occupation and cause of death. There was an excess of deaths from cancer of the lung and bronchus in workers in the printing trades as a group compared with the male population of the region in which they worked, adjusted for age and calendar year of death. The excess was about 30% in London and about 40% in Manchester. Both these excesses are significant at the 1% level. In Manchester, but not in London, there was a concentration of excess of lung cancer incidence in machine room men. White collar workers showed no difference between observed and expected deaths in London and only a small excess in Manchester. There were small deficits of deaths from bronchitis, about 10% for printing trade workers, and 30-40% for white collar workers, with little difference between London and Manchester. Neither deficit is significant at the 5% level because of the small numbers involved. This survey does not provide any evidence about the cause of the overall small excess of deaths from lung cancer, which might or might not be occupational. The larger excess in the Manchester machine room men is more likely to be due to an occupational hazard.

- 2755 THE CANCER PATTERN IN AFRICANS AT BARAGWANATH HOSPITAL, JOHANNESBURG. (E.) Robertson, M. A. (Natl. Cancer Ass. South Africa, Johannesburg), J. S. Harington and E. Bradshaw. *Brit J Cancer* 25(3):377-384, 1971.

Incidence, ratio, and tribal occurrence patterns are developed in this study. Statistical analysis of cancer cases admitted to Baragwanath Hospital during the period 1948-64 indicates a steady increase in the number of cancer cases. The overall cancer incidence for Johannesburg, as calculated from hospital records, is similar to the incidence determined in an earlier study. Despite this similarity in overall occurrence, the rate for esophageal cancer has doubled in males and increased five-fold in females. A slight increase in the rates of lung and prostatic cancer in males is seen; rates for female breast cancer have not changed appreciably. Decreases are seen in the incidence of cancer of the cervix, stomach and colon. A marked reduction is observed in the rate of incidence of liver cancer for both sexes. Ratio studies comparing hospital admissions for the periods 1950-54 and 1960-64 indicated that esophageal cancer had risen from 10.3% to 27.5% of all cancers in males, and that respiratory system cancer had risen from 8.9% to 11.7% in males. In females, the increase in cancer of the esophagus had shifted from 0.8% to 4.7% of all cancers reported, though the proportion of breast cancer remained stable. Undue frequency of certain types of cancers among specific tribes is noted. Rough estimates of tribal susceptibility were determined and analyses showed that members of the Tswana and Ndebele tribes had high overall cancer incidence; whereas Shangaan tribal members show low frequency, except for a high incidence of liver cancer. Finally, the high frequency of certain cancers in some tribes is attributed to susceptibility, tribal custom and environment.

- 2756 THE CANCER PATTERN IN AFRICAN GOLD MINERS. (E.) Robertson, M. A. (Natl. Cancer Ass. South Africa, Johannesburg), J. S. Harington and E. Bradshaw. *Brit J Cancer* 25(3):395-402, 1971.

The incidence of cancer at various sites among African gold miners is surveyed. During the period 1964-68 the crude cancer rate (50.9/100,000 man-yr) was unexpectedly high in light of the selective nature of the group observed. A survey population of over 1.8 million males who had passed three medical examinations preliminary to contracting for work, showed 923 cases of cancer. Verification of the malignancies was made by clinical and histologic diagnosis. The sites of greatest cancer frequency were the liver, esophagus, respiratory system and the bladder. Data analysis indicates 486 cases of liver cancer, with 69% of these occurring in persons from Mozambique and 12% occurring in persons from Transkei. Out of a total of 120 cases of esophageal cancer 68% occurred in persons from Transkei. Among the 50 respiratory cancer cases, 36% occurred among persons from Transkei. Finally, of the 46 cases of bladder cancer, 67% was found on persons from Mozambique. More than half of the cancer cases occurred in miners with less than five years of service, the greatest incidence occurring among males younger than

35 years. Analyses of the figures compiled by the geographical origin of the miners suggests that the high incidence of malignancies may be due to physical environment, tribal custom or a combination of both factors.

- 2757 MALIGNANT TUMORS IN INFANCY AND CHILDHOOD AS SEEN IN JAKARTA. (E.) Darmawan, S. (Med. Sch., U. Indonesia, Jakarta), Hidayatkusumawidjaja and J. H. Wirjadi. *Paediat Indonesia* 11:155-166, 1971.

Malignant tissues in all sites, identified by screening surgical specimens from pediatric patients in Jakarta, were accumulated over a 15-year period (1951-1965). Cases of childhood leukemia were excluded from the study. Out of a total of 83,744 tissues examined, tumors were identified in 393 cases. A low overall incidence (5.8%) of malignant tissue in the infancy-childhood period was seen. Within the group of children identified as having tumors, a higher frequency of occurrence in the age group two to four years of age was found, and the rate of incidence of all tumors among males (59.3%) exceeded that in females (40.7%). Analyses were carried out on the site incidence of malignant tissues. Results indicated that of all cases studied, 42.6% of tumors occurred in the region of the head, 25.3% occurred in the trunk, 17.9% were found in the region of the neck, and 14.2% were found in the extremities. The common sites of origin as found in these pediatric patients differed markedly from the malignant sites observed in adults; the common adult tumors, e.g. carcinoma of the breast, uterus, skin, lung and stomach, are rarely found in infancy and childhood.

- 2758 ETHNIC AND CONSTITUTIONAL DIFFERENCES AND THEIR RELATION TO BREAST DISEASES IN ISRAEL: EDUCATIONAL AND SOCIO-ECONOMIC STATUS. (E.) Bertini, B. (Cytol. Lab., Kupat Holim, Tel-Aviv, Israel), A. Ber, L. N. Posener and S. Zelikson-Singer. *Brit J Cancer* 25(3):428-440, 1971.

The incidence of breast disease and its relationship to ethnic origin, educational background, and socio-economic status of an Israeli group of women is studied. A population group which consisted of 1298 cases of mammary cancer and 1816 cases of benign mastopathy hospitalized during 1960-1964 was studied in parallel to a group of 10,604 controls. Incidence patterns vary: statistics show a breast cancer morbidity rate of 63.6/100,000 in women of Western origin, 36.3/100,000 in Israeli-born females, and 25.5/100,000 in women of Asian origin. Notable was the relationship between educational level and breast cancer incidence. Findings show that all Oriental groups with a low incidence of breast cancer but a higher incidence of benign mastopathy, maintained a low educational standard. Among the Western women, the incidence of breast cancer was significantly higher, as was the level of educational background. A comparison of socio-economic factors was determined according to the husband's occupation. Eastern women whose husbands were unskilled workers had a lower rate of breast

cancer, whereas in Western women whose husbands held professional positions, there was a high incidence of breast cancer. Comparisons of cancer incidence and the mean ages of the women, between ethnic groups of Eastern women and between immigrant mothers and their Israeli-born daughters is also considered.

- 2759 THE CANCER PATTERN IN AFRICANS OF THE TRANSVAAL LOWVELD. (E.) Robertson, M. A. (Natl. Cancer Ass. South Africa, Johannesburg), J. S. Harington and E. Bradshaw. *Brit J Cancer* 25(3):385-394, 1971.

The incidence and pattern of occurrence of cancer is reported in a four-district area of Transvaal lowveld. Data acquired in a six-year period (1962-67) indicate that tribal members in northern districts have a lower overall incidence of cancer than those in southern regions. It is suggested that the reduced cancer incidence is due to a susceptibility factor, with those residing in the southern regions having a generally higher susceptibility. Analyses of patterns of cancer types in tribes occupying the districts indicated that: 1) Sotho tribe members predominant in the north show a frequency of skin, bone and connective tissue tumors; 2) Swazi tribe members predominant in the south have a high incidence of liver and bladder cancer; 3) the Shangaan tribe members, evenly distributed over the study region, show far more cases of bladder cancer than is warranted by their proportion in the population. In males of the entire region there was a high rate of cancer of the liver and in females a substantial frequency of cancer of the cervix. Data are presented which compare frequency rates among populations in contiguous areas.

- 2760 RETINOBLASTOMA PROBLEMS IN THE NETHERLANDS. (E.) Schappert-Kimmijser, J. (Netherland Ophthal Soc., Amsterdam). *Ophthalmologica* 163:12-14, 1971.

Analysis of 563 cases shows bilateral retinoblastoma to have a hereditary incidence at a 50-100% rate and unilateral retinoblastoma at a 20% rate. Due to this genetic frequency, the surviving males and females of procreative age are being observed in a follow-up study to ensure the earliest possible detection of any case which might occur in their offspring. A separate investigation to establish the distinguishing characteristics between the hereditary and nonhereditary retinoblastomas is in progress. Pertinent Netherlands agencies and professionals are cooperating in this effort.

- 2761 GASTROINTESTINAL CANCER IN IRAN. (E.) Haghighi, P. (Dept. Path., Phalavi U., Shiraz, Iran) and K. Nasr. *J Chron Dis* 24(10):625-633, 1971.



The minimal incidence (pathologically proven cases in the total possible population) of gastrointestinal cancers in Southern Iran is compared to the true incidence of the same in Connecticut, which has a very complete tumor registry. Since the proven cases of cancer in Iran are less than its true incidence, it can be concluded that if the minimal incidence of a cancer in Southern Iran is greater than the true incidence of the same cancer in Connecticut, then the true incidence of this cancer in Southern Iran must be higher. Using this concept, it appears that most gastrointestinal cancers, with the exception of those of the pancreas and colon are most frequent in the younger population of Iran. Further, upper gastrointestinal cancers seem more frequent in Iran. The primary upper small intestinal lymphoma, a tumor rarely encountered in Western countries, is the most frequent small intestinal malignant tumor encountered in Iran. Reasons for the higher frequency of gastrointestinal cancers, especially in a younger population, remain unclear but may include a combination of genetic and environmental factors.

- 2762 A SURVEY OF NASOPHARYNGEAL TUMORS AMONG FILIPINOS: A REPORT OF 203 CASES. (E.) Pantangco, E. E. (Dept. Path., U. Santo Tomas, Philippines), G. F. Basa and M. Canlas. *J Philipp Med Ass* 46(2):60-73, 1970.

A study of 203 patients with histologically verified nasopharyngeal tumors is reported. Incidence and information data were acquired from the files of the pathology departments of three hospitals in Manila and from the Philippine Cancer Society. The statistical data represent a cross-sectional index of the population at risk, except that Chinese patients are not well represented. Tumor incidence among males is 70.93% and among females 29.07% for the cases reviewed. The majority of cases studied fall into the 41 to 50 year age bracket, while most cases reported in Western countries are in the 50 to 60 year age bracket. Clinically, there was a higher incidence of advanced cases among a younger age group (10 to 50) the youngest being 12 years and the oldest being 47 years. Local lesions were found in the 20 to 60 age range; the youngest in this group is 48 years and the oldest is 71 years. The effect of habits, occupational hazards, nutrition, coexisting disease and their causal significance in tumorigenesis is evaluated. An extensive summary of the geographic pathology, causative factors, anatomy, pathology, and modes of treatment is also included.

- 2763 OCCUPATION AND CANCER OF THE LOWER URINARY TRACT. (E.) Cole, P. (Harvard U. Sch. Public Hlth., Boston, Mass.), R. Hoover and G. H. Friedell. *Cancer* 29(5):1250-1260, 1972.

This study is designed to estimate the incident risk of bladder cancer as it is associated with specific occupations. Data based on case reports

of 461 persons with cancer of the lower urinary tract were compared to case reports of a control group series of 485 persons. The occupational categories for all persons in the test series are defined and adjusted for age and length of employment. Excessive risk patterns are found to exist in five specific occupation areas: 1) dye-stuffs; 2) rubber; 3) leather; 4) paint; and 5) organic chemicals. Data analyses showed that these categories accounted for 7.3/100,000 cases of urinary tract cancer in men of ages between 20-89 years of age and is considered to be significant. In addition, data provided insight into several occupations which had not been previously suspected as being hazardous. Simultaneous inquiry into the role of cigarette smoking as an aspect of occupational risk in cancer of the urinary tract indicated no correlation existed either directly or indirectly among clerical workers.

- 2764 SKIN CANCER: RELATIONSHIP TO TOPICALLY APPLIED HORMONES. (E.) Spoor, H. J. (New York, N.Y.). *Cutis* 9(3):335-342, 1972.

This analysis is derived from a review of 389 patients with skin cancer treated by a private practitioner. The histologically confirmed diagnosis and the treatment of 342 individuals is reported. Among 180 males and 162 females five types of skin cancer are reported: basal cell epithelioma (67.7% of cases), anaplasia in senile keratosis (19.4% of cases), squamous cell epithelioma (8.3% of cases), Bowen's disease (2.8% of cases) and malignant melanomas (1.7% of cases). In the total group, 209 cases are of the single lesion type, while 133 cases developed additional lesions during follow-up. Review of data indicated that if more than one lesion is going to develop in any individual, it will occur within two years after visualization of the primary lesion. Considerations of causal factors for this disease include age, excessive exposure to sunlight and previous exposure to sunlight and previous exposure to X-ray whether accidental or therapeutic. The effectiveness of topical therapy as treatment is evaluated only in relationship to those patients with multiple and repeat lesions. Following treatment lesions precipitated by X-ray exposure recurred more frequently. Analyses of data to determine the effectiveness of various topical compounds over a period of 10 years is presented in detailed tables. Conclusions drawn from this study are: 1) histopathological confirmation of diagnosis is essential; 2) single lesions occur more frequently; 3) most skin cancers arise from unknown causes; 4) topical treatment can best be evaluated in multiple lesion cases; and, 5) in non-X-ray cases topical treatment is most effective in reducing the frequency and delaying the onset of new lesions.

- 2765 CARCINOMA OF THE CERVIX IN SOUTHWESTERN AMERICAN INDIAN WOMEN. (E.) Jordan,

S. W. (U. New Mexico Sch. Med., Albuquerque), R. L. Sopher, C. R. Key, D. Brylinski and J. Huang. *Cancer* 29(5):1235-1241, 1972.

A study population of over 22,000 American Indian women is reviewed for the age-specific frequency of *in situ* and invasive carcinoma of the cervix. An equally large non-Indian group from the same region was used as a control group. Analysis of age distribution indicated that there are relatively fewer cervical carcinoma cases among Indians in the under-25-yr-old group than among non-Indians. The frequency of cervical smears by age indicates that among non-Indians a maximum rate is reached between 40-49th yr and then drops off, while among the Indian group is lower during the reproductive years and reaches a maximum in 60-yr and older individuals. A striking difference in the incidence of cancer between the two groups is noted. The Indian rate increased progressively with age, while the non-Indian group reached a maximum incidence during the fifth decade and subsequently declined.

Note is also made of the strikingly low incidence of cancer for 30-49 yr old Indian women as compared with other subjects. It is thought that this implies an operating factor in the Indian group which has not yet been identified. In light of the trends noted, it is suggested that environmental or behavioral patterns are of paramount importance in the development of cervical carcinoma.

2766 TONGUE CANCER: ANALYSIS OF CASES IN A 10 YEAR PERIOD AT U.A.M.C. (E.) Riggs, O. E. (U. Arkansas Med. Ctr., Little Rock). *J Arkansas Med Soc* 68:229-231, 1972.

Case histories of 34 patients with primary carcinoma of the tongue treated at the University of Arkansas Medical Center between 1959 and 1970 are reviewed and discussed. Of these patients 27 were male and 7 female, 27 were caucasian and 7 noncaucasian, and all were over 40 years old. Irradiation therapy was used on only 24 of the patients, four patients were given pre-operative irradiation, and one patient was given a planned postoperative course of irradiation therapy, with five additional patients being given postsurgical irradiation. All but two of the patients died within 18 months.

2767 DIETARY AFLATOXINS AND HUMAN LIVER CANCER. II. AFLATOXINS IN MARKET FOODS AND FOOD-STUFFS OF THAILAND AND HONG KONG. (E.) Shank, R. C. (Dept. Nutr., Massachusetts Inst. Tech., Cambridge), G. N. Wogan, J. B. Gibson and A. Nondasuta. *Fd Cosmet Toxicol* 10(1):61-69, 1972.

This survey is designed to determine whether aflatoxins are present in local food supplies to such an extent as to constitute a public health hazard. Sample foods analyzed are commonly found in the diet of persons residing in Thailand. In excess of 2100 samples of market foods were tested for

aflatoxin content. Assay was carried out by chloroform extraction, silica-gel clean-up of contaminants and quantitative estimation of aflatoxin B<sub>1</sub>, B<sub>2</sub>, and G<sub>2</sub> by fluorescence on thin layer chromatograms. Results indicated that 9.4% of all food samples tested contained detectable concentrations of aflatoxin. Peanuts and corn were shown to be principle vectors of the contaminant. Fish, the largest single source of protein in the Thai diet, contained moderate amounts of toxin. Rice and chili peppers, which are staple foods, contained negligible amounts of the contaminant. Geographical distribution of the contaminant showed highest mean aflatoxin concentrations in food stuffs from the region north of the Gulf of Thailand and from the central provinces. The information acquired in this survey is currently being utilized as the basis of an investigation into the possible relationship between dietary aflatoxin loads and the incidence of primary liver cancer in the Thai population.

2768 DIETARY AFLATOXINS AND HUMAN LIVER CANCER. III. FIELD SURVEY OF RURAL THAI FAMILIES FOR INGESTED AFLATOXINS. (E.) Shank, R. C. (Dept. Nutr., Massachusetts Inst. Tech., Cambridge), J. E. Gordon, G. N. Wogan, A. Nondasuta and B. Subhamani. *Fd Cosmet Toxicol* 10(1):71-84, 1972.

A field survey of aflatoxin consumption through cooked foods in three rural areas of Thailand and its possible effect on liver carcinoma is presented. Over a period of one year 144 randomly-selected households in nine representative villages participated in the study, allowing observations and food testing to be completed in two-day series three times during the year, to account for seasonal diet variations. Samples of foods eaten were assayed for aflatoxin content; total amount of aflatoxin ingested was determined by weighing food before and after a meal. Analysis of the data collected indicated considerable seasonal variation in toxin consumption. In the region of Singburi family toxin consumption was at its highest level during the rainy season, ranging from 73 to 81 mg total toxin/kg body weight/day. Persons in the Ratburi region showed high toxin consumption during the hot season, ranging from 45 to 77 mg total aflatoxin/kg body weight/day. Aflatoxin consumption in the Songkhla region was consistently small throughout the year, with no aflatoxin ingestion occurring among a majority of the household members during a major portion of the year. The extensive data accumulated and correlated to seasons, number of persons in the household, and types of foods consistently eaten, are considered to be critical preliminary data. Further studies demonstrating the relationship of aflatoxin ingestion and human liver disease incidence are in process.

2769 THE INCIDENCE OF LUNG CANCER IN THE U.S. SINCE 1955 IN RELATION TO THE ETIOLOGY OF THE DISEASE. (E.) Sterling, T. D. (Dept.



Appl. Math., Washington U., St. Louis, Mo.) and S. V. Pollack. *Amer J Public Hlth* 62(2):152-158, 1972.

The effect of carcinogenic air pollutants on lung cancer deaths in the U.S. is discussed. Data on the number of deaths from lung cancer are obtained from the *Vital Statistics of the United States, 1955 to 1966* and population figures were derived from census reports. Analysis is made by using three different indicators: 1) Calculating population data for each year by age and sex on the basis of the reciprocal of the death rates for that year; 2) Computation of the proportion of all deaths due to lung cancer by age and sex; 3) The proportion of all malignancies due to lung cancer by age and sex. Calculations indicated that in age groups over 55 yr there appeared to be an increase in the lung cancer rate. Between the ages of 25 to 54 years lung cancer rates have apparently stabilized. In persons younger than 25 years a definite decline in the rate of lung cancer is seen. The death rate due to lung cancer in males is consistently higher than in females; with males exposure to environmental factors such as particulate matter a possible factor in this regard. The analyses and observations presented are intended to add impetus to the necessity for speedy implementation of effective clean air programs, and may suggest that particulate pollution rather than smoking may be the primary agent of lung cancer in the U.S.

- 2770 EPIDEMIOLOGY OF EPIDERMAL CARCINOMA OF THE VULVA. (E.) Franklin, E. W. (U. Texas, MD Anderson Hosp. Tumor Inst., Houston) and F. D. Rutledge. *J Obstet Gynec* 39(2):165-172, 1972.

This investigation describes epidemiologic factors among 249 patients seen for consultation and treatment at the MD Anderson Hospital from 1944 to 1968. Review of records indicated that 206 patients had invasive carcinoma of the vulva and 43 patients had squamous carcinoma in situ. An analysis of age at the time of treatment revealed that carcinoma in situ of the vulva occurred during the fifth and sixth decades while invasive carcinoma occurred at a median age of 63 years. Of 235 patients available for review, 29 were classified as luetic either by past history or serological testing. Syphilis was diagnosed with equal frequency in both types of cancer, occurring in 13% of both categories. Though numbers are small, 16 Negro luetic patients averaging 47 years in age were younger than 28 Negroes without lues who averaged 53 years of age. Findings showed 95% of all patients had been married, and 25% of the total group were nulliparous. Of the 133 patients in the series who experienced spontaneous or surgical menopause at a known age, 19% underwent this change before age 41 and 54% by age 45. The early age of menopause is thought to reflect associated pelvic disease rather than a primary etiologic factor in vulvar carcinoma. Long pretreatment period of pruritis, bleeding and vulvar pain was noted in patients with alarming frequency, emphasizing the need for increased medical education among women. Coincidental to the age factor noted

is a high incidence of obesity, hypertension and diabetes among these patients. It is suggested that despite their infrequent occurrence, the accessibility of the lesions to study and diagnosis would allow better treatment if patient and physician delay could be avoided.

- 2771 CIRRHOSIS AND PRIMARY (LIVER CANCER) CARCINOMA INCIDENCE IN IRAN. (E.) Armin, K. (U. Tehran, Iran). *Acta Med Iranica* 13(3-4):85-101, 1970.

A report of the incidence of primary carcinoma of the liver in Iran is presented. Autopsy data for the period 1960-68 is reviewed as it was accumulated at the Tehran University Hospital. Out of a total of 4389 autopsies performed, 653 cases with hepatic lesions are identified. Data analyzed in these cases included; illnesses antecedent (especially hepatitis or jaundice), first clinical manifestation during last admittance to the hospital, and cause of death. Results showed that in 653 hepatic lesions 37.5% of the cases presented acute and chronic inflammatory conditions, 20.5% were metastatic carcinoma. The study includes extensive documentation of these incidences, with primary site of lesion, age, sex, nutritional patterns, alcohol consumption, opiate use, and previous medical conditions. Gross and microscopic findings at the time of autopsy are also presented.

- 2772 AN EPIDEMIOLOGIC TEST OF THE "SPECTRUM OF DISEASE" CONCEPT IN CERVICAL NEOPLASIA. (E.) Hulka, B. S. (Dept. Epid., U. North Carolina, Chapel Hill) and L. L. Kupper. *J Natl Cancer Inst* 47(6):1215-1222, 1971.

- 2773 A PROPORTIONAL MORTALITY STUDY OF A GROUP OF NEWSPAPER WORKERS. (E.) Greenberg, M. (Med. Serv. Div., Dept. Empl., London, England). *Brit J Industr Med* 29(1):15-20, 1972.

- 2774 BREAST CANCER RISK FOLLOWING A MAJOR SALIVARY GLAND CARCINOMA. (E.) Dunn, J. E., Jr. (St. Calif., Dept. Public Hlth., Berkeley), K. U. Bragg, C. Sautter and C. Gardipee. *Cancer* 29(5):1343-1346, 1972.

- 2775 SKIN CANCER IN LEBANON. (E.) Shbaklu, Z. (Amer. U. Med. Ctr., Beirut, Lebanon) and A. K. Kurban. *Leb Med J* 23(6):583-589, 1970.

- 2776 SOME ASPECTS OF CANCER OF THE STOMACH IN LEBANON. (E.) Gedeon, E. M. (Central Public Hlth. Lab., Beirut, Lebanon). *Leb Med J* 23(6):527-536, 1970.

- 2777 ENDEMIC NEPHRITIS AND URINARY TRACT CANCER IN YUGOSLAVIA, BULGARIA AND RUMANIA. (E.) Markovic, B. (Med. Ctr., Gnjilane, Yugoslavia). *J Urology* 107:212-219, 1972.
- 2778 HISTOLOGIC TYPES OF GASTRIC CARCINOMA AMONG KOREANS. (E.) Kim, K. H. (Dept. Clin. Path., Woo Sok U., Seoul, Korea), C. H. Chi, S. K. Lee, D. Lee and T. Kubo. *Cancer* 29(5):1261-1263, 1972.
- 2779 SOCIAL EPIDEMIOLOGY OF CANCER OF THE TESTIS. (E.) Graham, S. (Dept. Social Preventive Med., St. U. New York, Buffalo) and R. W. Gibson. *Cancer* 29(5):1242-1249, 1972.
- 2780 MALIGNANT TRANSFORMATION HAZARD OF THE ENDEMIC GOITER IN URBAN ENVIRONMENT. (Rum.) Mandache, Fl. (Brincoveanu Hosp., Bucharest, Rumania), V. Prodescu, I. Lutescu, L. Stratulat, I. Georgescu, P. Babaca and I. Curea. *Stud Cercet Endocr* 22(6):459-464, 1971.
- 2781 INCIDENCE OF LUCKE RENAL ADENOCARCINOMA IN RANA PIPPIENS AS DETERMINED BY HISTOLOGICAL EXAMINATION. (E.) Marlow, P. B. (Dept. Anat., Georgetown U., Washington, D.C.) and S. Mizell. *J Nat Cancer Inst* 48(3):823-829, 1972.
- 2782 PRIMARY CARCINOMA OF THE VAGINA. (E.) Daw, E. (Dept. Obst., Dundee U., Scotland). *J Obstet Gynaec Brit Comm* 78:853-856, 1971.
- 2783 SURVIVAL OF BREAST CANCER PATIENTS RELATED TO INCIDENCE RISK FACTORS. (E.) Morrison, A. S. (Harvard Sch. Public Hlth., Boston, Mass.), C. R. Lowe, B. MacMahon, J. H. Warram, Jr. and S. Yuasa. *Int J Cancer* 9(3):470-476, 1972.
- 2784 METHODICAL STUDY FOR THE COLLECTION OF EPIDEMIOLOGICAL DATA OF MAMMARY CARCINOMA IN THE G.D.R. (Ger.) Möpert, S. (Med. Clin., Humboldt U., Berlin, Germany) and K. Baldauf. *Rad Biol Ther* 12(3):319-324, 1971.
- 2785 SOME EPIDEMIOLOGIC VARIABLES IN OVARIAN CARCINOMA. (E.) Krain, L. S. (Dept. Med., U. California, Los Angeles). *HSMHA Health Reports* 87(1):56-60, 1972.
- 2786 LUNG CANCER. (Sp.) Galarce, J. A. (No affiliation), R. Slutzky, R. S. Suarez and C. A. Lavigne. *Sem Med* 139(14):431-446, 1971.
- 2787 CARCINOMA OF THE OESOPHAGUS AFTER GASTRIC SURGERY. (E.) Stalsberg, H. (Ullevål Hosp., Oslo, Norway). *Lancet* (7746):381, 1972.
- 2788 EPIDEMIOLOGICAL APPROACH TO MALIGNANT MELANOMA. (E.) Anonymous. *Brit Med J* 1(5793):130, 1972.
- 2789 CANCER MORTALITY IN NEW ZEALAND: 1. GENERAL. (E.) Donovan, J. W. (Dept. Math. Statistics, U. Sydney, Australia). *N Z Med J* 72(458):9-12, 1970.
- 2790 EPIDEMIOLOGICAL ASPECTS OF ORAL CANCER. (E.) Ferrell, R. L. (No affiliation), W. S. Carter and C. T. Yarrington, Jr. *Eye Ear Nose Throat Monthly* 50(11):423-428, 1971.
- 2791 TOBACCO AND CANCER: EPIDEMIOLOGIC PROBLEMS. (Fr.) Garbe, E. (No affiliation). *Vie Med* 52(30):3453,3454,3457-3460,3462, 1971.
- 2792 CONTRIBUTION OF EPIDEMIOLOGY IN THE PREVENTION OF CANCER. (Fr.) Hayat, M. (No affiliation). *Vie Med* 52(30):3463,3467-3468, 1971.
- 2793 ON THE EPIDEMIOLOGY OF BREAST CANCER IN WOMEN. (Ger.) Sachs, H. (U. Womens' Clin., Hamburg-Eppendorf, Germany) and H. Maass. *Deutsch Med Wschr* 96(44):1701-1707, 1971.
- 2794 EPIDEMIOLOGICAL AND GEOGRAPHICAL EVALUATION OF THE OCCURRENCE OF NEOPLASTIC DISEASES IN THE PINCZOW DISTRICT IN 1960-69. (Pol.) Sznajd, J. (Sci. Res. Inst. Med. Krakow, Poland), A. Filipek, A. Hartwick, T. Janus, M. Magdon and M. Mysik. *Przegl Lek* 28(11):480-484, 1971.
- 2795 CANCER MORTALITY IN SKOPJE 1961-1969. (Ger.) Gjorgov, A. (City Pub. Hlth. Inst. Skopje, Yugoslavia). *Lij Vjes* 93(5):517-532, 1971.
- 2796 RETICULUM CELL SARCOMA IN SENEGAL (WITH REFERENCE TO 30 CASES). (Fr.) Simaga, D. (No affiliation), P.-A. Menye, A. Sanou and D. Diop. *Bull Soc Med Afr Noire Lang Franc* 16(2):142-144, 1971.
- 2797 MINERAL OIL CANCER IN BRITAIN. (E.) Row, F. J. C. (Chester Beatty Res. Inst., London, England). *Arq Patol Geral Anat Patol* 11:165-171, 1971.



- 2798 PRIMARY MALIGNANT TUMOURS OF THE SMALL INTESTINE. (E.) Vuori, J. V. A. (Dept. Surg., U. Turku, Finland). *Acta Chir Scand* 137(6):555-561, 1971.
- 2799 OBSERVATION ON THE EPIDEMIOLOGY OF BREAST CANCER 1971. (E.) Macdonald, E. J. (M. D. Anderson Hosp. Tumor Inst., Houston, Texas). *Cancer Bull* 23(6):102-106, 1971.
- 2800 CONTRIBUTION TO THE EPIDEMIOLOGY OF PLEURAL MESOTHELIOMA. (Ger.) Bittersohl, G. (Occupational Hyg. Ctr. Chem. Ind. Leuna, Germany) and H. Ose. *Z Ges Hyg* 17(11):861-864, 1971.
- 2801 CANCER OF THE FEMALE GENITAL ORGANS IN ALGERIA. (Fr.) Bonafos, M. (No affiliation), R. Le Cannelier, El Okbi, O. Larbi and A. Boudiaf. *Med Afrique Noire* 18(7):625-628, 1971.
- 2802 CANCER EPIDEMIOLOGY: METHOD OF STUDY. (Ser.) Jurukovski, J. (Med. U. Skopje, Yugoslavia). *God Zbor Med Fak Skopje* 17:259-266, 1971.
- 2803 BRONCHIAL CARCINOMA IN THE NECROPSY MATERIAL OF SZCZECIN VOIVODSHIP, IN 1949-1968. (Pol.) Dominiczak, K. (Dept. Path. Anat. Szczecin Hosp., Poland). *Gruzlica* 39(9):885-890, 1971.
- 2804 PRIMARY BRAIN TUMOR EPIDEMIOLOGY IN MEXICO. (Sp.) Olivares, L. (20 November Hosp. Ctr. Mexico City, Mexico), M. Alter, L. Marquez, L. Cisneros and C. Sanchez. *Salud Publica Mex* 13(3):305-312, 1971.
- 2805 FREQUENCY AND DISTRIBUTION OF LEUKEMIA AT THE NANCY U.H.C. IN 1970. (Fr.) Streiff, F. (Reg. Blood Transf. Ctr. Nancy, France), A.-M. Gehin, J.-C. Humbert, J. Buisine and F. Martin. *Ann Med Nancy* 11:197-203, 1972.
- 2806 FERTILITY AND CARCINOMA OF THE FEMALE GENITAL ORGANS. (Sp.) Garcia, N. L. (Natl. Cancer Inst., Madrid, Spain) and L. L. De La Osa. *Toko Ginec Pract* 31(303):247-250, 1972.
- 2807 FERTILITY AND EXTRAGENITAL CARCINOMA. (Sp.) Sanchez, S. R. (Natl. Cancer Inst., Madrid, Spain) and L. De La Osa. *Toko Ginec Pract* 31(303):251-254, 1972.
- 2808 STERILITY AND MULTIGRAVIDITY AS RELATED TO CARCINOMA OF THE UTERINE CERVIX. (Sp.) Caballero, R. G. (Natl. Cancer Inst. Madrid, Spain) and A. R. Rodriguez. *Toko Ginec Pract* 31(303):255-262, 1972.
- See also:
- \* (Rev): 2223, 2250, 2269, 2298
  - \* (Chem): 2408
  - \* (Path): 2741

- 2809 CYTOGENETIC STUDIES IN ACUTE MYELOID LEUKAEMIA. (E.) Jensen, M. K. (U. Hosp., Copenhagen, Denmark). *Acta Med Scand* 190:429-434, 1971.

Results of cytogenetic studies conducted between September 1964 and December 1970 on bone marrow aspirates from 50 patients with acute myelogenous leukemia (AML) are reported; a brief review of some cytogenetic literature on AML is also presented. Of the 50 patients studied 22 had abnormal stem lines in the bone marrow, with the other 28 having a diploid chromosome complement. The chromatin in most metaphases obtained in relapse from all patients appeared blurred and the chromatid boundary was ill-defined. In 19 of 44 patients studied before therapy with cytostatics structural chromosome abnormalities were found; these were almost entirely chromatid breaks. Hypodiploid and hyperdiploid stem lines were found to occur with approximately equal frequency in AML patients; pseudodiploid clones were rarely found. It is suggested that the bone marrow metaphases with blurred chromosomes comprise the leukemic cell population and that the metaphases having normal chromatin are remnants of a nonleukemic population. Erythropoiesis in AML may not be normal but may be a direct result of the leukemic process, as evidenced by the same abnormal chromosome complement in the myeloblasts and erythroblasts of AML patients. Data from cytogenetic studies also indicate that abnormal stem lines in AML do not arise terminally but are present very early in the course of the disease.

- 2810 MERCURY DERIVATIVES OF THE FAB AND FC FRAGMENTS OF A HUMAN MYELOMA PROTEIN. (E.) Steiner, L. A. (Dept. Biol., Massachusetts Inst. Tech., Cambridge) and P. M. Blumberg. *Biochem* 10(25):4725-4739, 1971.

Divalent mercury ion ( $\text{Hg}^{2+}$ ), a bifunctional reagent highly specific for sulfhydryl groups, was used to study the role of interchain bridges in the structural organization of IgG1 myeloma protein. The development of a generally applicable method for preparing heavy metal derivatives of immunoglobins or other proteins for x-ray diffraction was also attempted. Myeloma protein and its Fab and Fc fragments were characterized by DEAE-cellulose chromatography, Sephadex G-100 gel filtration, polyacrylamide gel electrophoresis and zone electrophoresis.  $\text{Hg}^{2+}$  was bound to partially reduce Fc fragments with a saturation point of approximately two moles  $\text{Hg}^{2+}$ /mole Fc, with no  $\text{Hg}^{2+}$  binding to unreduced Fc fragments. It was concluded that the binding sites were the two disulfide cross bonds of the Fc chains, probably with a configuration of the type S-Hg-S. Physical and antigenic properties of Hg-bound Fc were the same as those of native Fc. X-ray diffraction analysis of Fc-Hg fragments revealed patterns quite similar to those of native Fc although the Fc-Hg crystals were not isomorphous with native crystal as the disulfide bonds were altered by the  $\text{Hg}^{2+}$  atoms. Dissociating solvents reduced the

Fc-Hg fragments to monomers. Titration of Fab with  $\text{Hg}^{2+}$  produced results analogous to those with Fc titration, with saturation at 0.8 mole  $\text{Hg}^{2+}$ /mole Fab. Fab-Hg and native Fab were indistinguishable physically and antigenically. SDS-polyacrylamide gel electrophoresis of Fab-Hg showed that the major components corresponded to the monomer or dimer of Fc, to native Fab and to the dimer of the light chain when Fab-Hg was in a dissociating solvent. Exposure of  $^{203}\text{Hg}^{2+}$ -protein to either unlabeled  $\text{Hg}^{2+}$  or to cysteine could completely dissociate both Fc-Hg and Fab-Hg. The  $\text{Hg}^{2+}$ -sulfur bond, however, was generally stable to a number of reagents in nondissociating solvents.

- 2811 LACK OF SIGNIFICANT ONCOGENICITY OF BIOLOGICAL PRODUCTS IN HAMSTERS. (E.) Cox, C. B. (Natl. Inst. Hlth., Bethesda, Md.), J. Landon, M. G. Valerio, A. Palmer, R. L. Kirschstein and S. H. Singer. *Appl Microbiol* 23(4):675-678, 1972.

A study was designed to screen biological products to determine whether any are oncogenic in newborn Syrian hamsters. Biological substances used for inoculation included live and inactivated viral vaccines, inactivated rickettsial and bacterial vaccines, toxoids, and a multiple bacterial antigen product. Simian virus 40, human adenovirus 12, and fluid from uninoculated control bottles of cell cultures were used as controls. Hamsters were injected s.c. with 0.1 ml of a biologic product within 24 hr of birth. The animals were weaned 21 days after birth, and observed weekly. Tumors were found in 228 of 7,643 animals inoculated with test materials and examined histologically, an incidence of 3%. Of these, 80 were adrenal cortical adenomas and the remainder (1.9%) were a variety of other tumors. In the surviving uninoculated control animals, 19 of 403 animals (4.7%) had tumors. Of these, ten were adrenal cortical adenomas and nine were of other types. None of the tumors were associated with the inoculation site or with inoculation of any particular product. It is concluded that the tumors in the inoculated animals were spontaneous.

- 2812 NEW SPECIES OF RAPIDLY HYBRIDIZING RNA IN CONTACT-INHIBITED AS WELL AS TRANSFORMED HAMSTER CELL LINES. (E.) Levine, A. S. (Natl. Cancer Inst., Bethesda, Md.), M. N. Oxman, H. M. Eliot and P. H. Henry. *Cancer Res* 32(3):506-510, 1972.

The rapidly hybridizing RNA sequences transcribed in primary hamster embryo cells and in lines of serially propagated hamster cells are compared by the technique of RNA-DNA hybridization-competition. Such sequences are known to be transcribed from reiterated DNA sites. The cells examined included line 1808 (SV40 transformed containing both S and T antigens and virus-specific RNA and DNA), line 1807 (SV40 transformed, containing S antigen and no detectable virus-specific RNA or DNA),



line 1807 (SV40 transformed, containing S antigen and no detectable virus-specific RNA or DNA), line 1809 (spontaneously transformed), lines 1802 and 1804 (both untransformed from the same pool of cells as lines 1807, 1808, and 1809 but never exposed to SV40), and line BHK 21 (continuous hamster cell line). Paired preparations of radiolabeled and unlabeled RNA from each cell line were obtained. Freshly excised adult Syrian hamster liver was used for the preparation of DNA. Unlabeled RNA from line 1804 competed completely with labeled RNA from SV40-transformed line 1808, indicating that there were no detectable, rapidly hybridizing RNA sequences transcribed in the transformed cells that were not also present in untransformed, contact-inhibited cells. However, unlabeled RNA from primary hamster embryo cells competed with only 62-66% of the hybridizable radioactivity present in RNA from line 1808, indicating the presence of hybridizing RNA sequences in SV40-primary hamster embryo cells that were not detectable in primary hamster embryo cells. RNA from either line or primary hamster embryo cells competed equally well in hybridization to Syrian hamster DNA, showing that there are no rapidly hybridizing RNA sequences detectable in primary hamster cells not also present in the SV40-transformed cells. Competition of labeled RNA from line 1804 with unlabeled RNA from either line 1804 or 1808 indicated that the rapidly hybridizing RNA's from lines 1804 and 1808 were identical. Competition experiments also revealed no differences between RNA's from lines 1802, 1809, 1807 and BHK 21. These results indicate that the acquisition of oncogenicity is not necessarily correlated with the appearance of new, rapidly hybridizing RNA sequences, since such new sequences may already be present in untransformed, serially propagated cells.

- 2813      ENDORIBONUCLEASE ACTIVITY ASSOCIATED WITH NUCLEOLAR RIBONUCLEOPROTEIN PARTICLES FROM NOVIKOFF HEPATOMA. (E.) Prestayko, A. W. (Baylor Coll. Med., Houston, Texas), B. C. Lewis and H. Busch. *Biochim Biophys Acta* 269(1):90-103, 1972.

Ribonucleoprotein (RNP) particles were extracted from nucleoli from Novikoff hepatoma ascites cells maintained in male Holtzman rats. Analysis of the nucleolar RNP by sucrose density gradient centrifugation revealed a slowly-migrating 78-S peak and a faster-migrating 110-S peak. Examination by electron microscopy showed that these particles were similar, being electron opaque, spherical and having a diameter of 200-300 Å. Paper chromatographic analysis of hydrolysates of <sup>32</sup>P-labeled RNA extracted from the 78-S RNP showed a nucleotide composition of AMP 12%, UMP 21%, GMP 36%, and CMP 30% which agreed well with the previously reported nucleotide composition of nucleolar preribosomal 28-S RNA. When nucleolar <sup>3</sup>H-labeled 45-S RNA was incubated with 78-S RNP particles at either 25 or 37°C for 15 min, marked degradation of the 45-S RNA occurred when analyzed on sucrose gradients and compared with controls incubated without 78-S RNP. Ribonuclease activity was completely destroyed by heating the ribonucleoprotein (RNP) particles at 100°C for ten min at pH 7.4. Neither 60-S nor 40-S ribosomal RNP subunits showed ribonuclease

activity toward 45-S RNA. Treatment of 78-S RNP with 8 mM EDTA had no effect on ribonuclease activity. Double treatment of 78-S RNP with 0.5% deoxycholate released less than 30% of the ribonuclease. 45-S, 28-S and 18-S RNA's were each incubated (25°C, 15 min) with 78-S RNP particles and the degradation products were analyzed by sucrose gradient centrifugation. Degradation products of 45-S RNA sedimented in the 10-16S region and those of both 28-S and 18-S RNA sedimented in the 15-20S region. Some of the 18-S RNA was apparently undegraded. Nucleolar 78-S RNP proteins were extracted with chlorethanol and were analyzed by polyacrylamide gel electrophoresis. None of the 20 bands which resulted showed ribonuclease activity. Extraction with LiCl without urea preserved ribonuclease activity and yielded fewer protein bands upon electrophoresis.

- 2814      A UNIQUE FORM OF CIRCULATING INSULIN IN HUMAN ISLET CELL CARCINOMA. (E.) Gorden, P. (Nat'l. Inst. Arthritis Metab. Dis., Bethesda, Md.), P. Freychet and H. Nankin. *J Clin Endocr* 36(6):983-987, 1971.

The circulating insulin components obtained from a patient with islet cell carcinoma were partially characterized. A comparison between a tumor-free patient and the islet cell tumor patient showed the proinsulin-like component to be larger in size and less reactive by radioimmunoassay, but more reactive by bioassay. The insulin component was otherwise indistinguishable from the non-tumor component. Whether this proinsulin-like component was a specific mutation or merely a more primitive form is uncertain.

- 2815      HUMAN LEUKEMIC CELLS: *IN VITRO* GROWTH OF COLONIES CONTAINING THE PHILADELPHIA (Ph<sup>1</sup>) CHROMOSOME. (E.) Chervenick, P. A. (U. Pittsburgh Sch. Med., Pa.), L. D. Ellis, S. F. Pan and A. L. Lawson. *Science* 174(4014):1134-1136, 1971.

Bone marrow cells and blood leukocytes were obtained from seven patients with typical chronic myelocytic leukemia (CML); the patients were known to have the Ph<sup>1</sup> chromosome in marrow cells. In four patients the CML was in relapse, in two the CML had undergone acute blastic transformation, and one patient was recovering from busulphan therapy and was pancytopenic. Marrow and blood cells were established in cultures; after 10-14 days of incubation, cells were prepared for microscopic scoring of metaphases for presence or absence of the Ph<sup>1</sup> chromosome. Cell colonies grew from blood or bone marrow cells from five of the seven patients; colony size was abnormally small. In colonies which contained metaphases which could be scored for the Ph<sup>1</sup> chromosome, cells were either Ph<sup>1</sup> positive or Ph<sup>1</sup> negative. No colonies contained mixed populations of Ph<sup>1</sup> positive and Ph<sup>1</sup> negative cells. The Ph<sup>1</sup> chromosome could not be identified in any metaphase of cells from the pancytopenic patient. The

finding that colonies contained either Ph<sup>1</sup> positive or Ph<sup>1</sup> negative cells suggests that a mixed population of leukemic and normal cells exists in the marrow of CML patients throughout the course of the disease.

- 2816 PROPERTIES OF THE GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE FROM EHRLICH ASCITES TUMOR CELLS. (E.) Mamaril, F. P. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.) and S. Green. *Arch Biochem* 147(2):583-587, 1971.

Glyceraldehyde-3-phosphate dehydrogenases from rabbit muscle, yeast and Ehrlich ascites tumor cells were inactivated by trypsin at 25° to the extent of 4, 25, and 46%, resp. The enzyme from Ehrlich ascites cells was 50% inactivated within two min when incubated with 1.0 mM ATP at 25° and was completely inactivated at 0°. Raising the temperature to 25°, resulted in a recovery of 50% of the original enzyme activity. The addition of NAD<sup>+</sup> to the system was required for recovery of the total activity. Sucrose density centrifugation showed two active components from the Ehrlich ascites cell enzyme. One was a 7.2-S component, sedimenting at the same rate as the rabbit muscle enzyme (140,000 daltons) and the other, a 4.4-S component (70,000 daltons). Addition of NAD<sup>+</sup> converted the 4.4-S component into the 7.2-S component and protected the enzyme from inactivation by ATP. These results suggest that the partial inactivation of the Ehrlich ascites enzyme was due to the dissociation of the 4.4-S component to inactive subunits and that its sensitivity to inactivation by trypsin may also be due to this 4.4-S component.

- 2817 HYPERPLASTIC AND INFLAMMATORY NODULES IN THE CANINE MAMMARY GLAND. (E.) Cameron, A. M. (Dept. Path., U. California, Davis) and L. J. Faulkin, Jr. *J Nat Cancer Inst* 47(6):1277-1288, 1971.

Techniques developed for demonstrating hyperplastic lesions in mammary glands of rodents were applied to whole mammary glands of untreated female beagle dogs. Eight purebred female beagle dogs from 7.6 to 8.5 years old at the time of necropsy were used; the dogs were sacrificed during the late metestrus or early anestrus stage of the estrous cycle. The mammary glands were removed from the skin after 24 hours' fixation in 10% buffered neutral formalin. All atypical nodules, readily seen under the dissecting microscope, were photographed and excised from the gland with adjacent glandular elements. Histologic examination was made of the 763 atypical nodules found; these were classified as normal, inflammatory or proliferative, with proliferative lesions being subclassified as hyperplastic or neoplastic. More atypical nodules were found in the combined posterior-2 glands than in the combined anterior-2 glands in all dogs. Diffuse epithelial hyperplasias comprised 56% of the total atypical glandular

nodules; more diffuse epithelial hyperplastic lesions were found in the posterior than in the anterior glands. It is believed that these may be of future value in the detection of mammary gland lesions in the dog.

- 2818 IN VITRO BINDING OF PROGESTERONE BY THE HUMAN ENDOMETRIUM DURING THE MENSTRUAL CYCLE AND BY HYPERPLASTIC, ATROPHIC, AND CARCINOMATOUS ENDOMETRIUM. (E.) Haukkamaa, M. (Steroid Res. Lab., U. Helsinki, Finland), O. Karjalainen and T. Luukkainen. *Amer J Obstet Gyn* 111(2):205-210, 1971.

A study of the specific progesterone-binding capacity of human endometrium *in vitro* during the normal menstrual cycle and in some pathologic conditions is reported. Endometrial material included specimens from the proliferative and secretory phases of the menstrual cycle, specimens of atrophic endometrium, specimens of simple endometrial hyperplasia, and specimens of endometrial carcinoma of varying degrees of differentiation. Progesterone-binding capacity of specimens was studied by an equilibrium dialysis method. Nonspecific binding by endometrial proteins was also studied; in non-specific binding studies, specimens of endometrium were also dialyzed against human albumin solution. The highest progesterone binding rates were seen in specimens of endometrium from the late proliferative phase of the menstrual cycle; samples from the secretory phase showed levels of progesterone binding similar to those seen in proliferative samples. Atrophic endometrium appeared to be devoid of specific progesterone-binding capacity. The highest binding rates for hyperplastic specimens were similar to rates of proliferative phase endometrium. There was no correlation between rate of progesterone-binding and degree of hyperplasia. Two endometrial carcinoma specimens were inactive while the highest binding rates observed in carcinoma specimens were comparable to rates in hyperplastic or proliferative endometrium. No correlation was seen between progesterone-binding capacity and degree of tumor differentiation.

- 2819 SELECTIVE INHIBITION OF TRANSFORMED CELLS IN CULTURE BY ANTI-THYMIDINE ANTIBODIES. (E.) Liebeskind, D. S. P. (Coll. Physicians Surg., Columbia U., New York, N.Y.), K. C. Hsu, B. F. Erlanger and S. M. Beiser. *Nature New Biol* 234(47):127-128, 1971.

Antithymidine antibody was used to determine whether DNA-reactive antibodies selectively inhibited transformed cells. Normal and methylcholanthrene-transformed Chinese hamster lung cells were grown at 37°C for four days. It was found that the normal cells did not take up antibody or normal gamma globulin when cultured for two to 72 hr. The transformed cells grown in the presence of fluoresceinated anti-thymidine antibody showed marked cytoplasmic perinuclear



fluorescence which was clumped and granular; the fluorescence was noted two hr after the fluorescent antibody was introduced and increased up to 48 hr. Normal gamma globulin was found to enter the neoplastic cells but did not disturb cell growth, while the anti-thymidine antibody did inhibit cell division. It is suggested that the observed perinuclear localization of antibody is a result of its reaction with nucleic acids migrating from the nucleus, thus inhibiting multiplication.

2820 MULTIPLE MALIGNANT TUMORS ASSOCIATED WITH PRIMARY CARCINOMA OF THE OVARY. (E.)

Silverman, B. B. (U. Pennsylvania Sch. Med., Philadelphia), R. T. O'Neill and J. J. Mikuta. *Surg Gynec Obstet* 134(2):244-248, 1972.

This investigation was undertaken to determine whether or not endometrioid carcinoma differs from other malignant lesions in the development of either synchronous or metachronous tumors. Four hundred and thirteen patients with primary carcinoma of the ovary are included in the study; 363 of these were diagnosed and treated within the period 1948-68. Only those patients having at least one year of follow-up data are included. There were 37 patients with multiple neoplasms in the total group studied. Of these, 17 had synchronous tumors of the endometrium and 20 had metachronous tumors occurring most commonly as adenocarcinoma of the breast. There was no evidence that race, parity or treatment of the original cancer influenced the incidence of multiple tumor growth. The high incidence of pathologic involvement of the breast and endometrium in patients with endometrioid carcinoma of the ovary is taken as a possible indication of hormonal involvement.

2821 STUDIES ON POLYPHENYLALANINE SYNTHESIS WITH A CELL-FREE SYSTEM OF RAT LYMPHOSARCOMA.

(E.) Koka, M. (Dept. Biochem., U. Chicago, Ill.) and T. Nakamoto. *Biochim Biophys Acta* 262(3):381-392, 1972.

Polyphenylalanine synthesis, Phe-tRNA binding and GTP binding and hydrolysis effected by rat lymphosarcoma ribosomal 40-S and 60-S subunits was studied. Female albino Sprague-Dawley rats (75-100 g) were used as hosts for Murphy-Sturm Lymphosarcoma; ribosomal subunits were isolated by ethanol and  $Mg^{+2}$  precipitation and sucrose gradient centrifugation. A high level of polyphenylalanine synthesis was found only when sucrose gradient fractions containing 40-S and 60-S subunits were combined. Phe-tRNA binding studies indicated that maximal binding occurred only when the supernatant protein, T1, and GTP were present; the T2 protein did not stimulate the reaction. The lymphosarcoma ribosomes showed a T1-dependent uncoupled GTPase activity which required the presence of both 40-S and 60-S subunits. When the 60-S subunit was missing GTP was bound without hydrolysis to the 40-S subunit, as was Phe-tRNA. Heparin was found to inhibit Phe-tRNA binding to the 40-S subunit; it also

inhibited the T1-catalyzed GTPase activity. Further studies are being performed to assess the role of GTP in aminoacyl-tRNA binding.

2822 EXPERIMENTAL STUDY OF A NEW MALIGNANT HUMAN TUMOR OF THE ASCENDING COLON IN LONG-TERM ORGANOTYPIC CULTURE. (Fr.) Wolff, E. (Inst. Exp. Embryol. CNRS, Nogent-sur-Marne, France), J. Smith and E. Wolff. *C R Acad Sci [D] (Paris)* 274(1):341-345, 1972.

Fragments of a malignant human tumor of the ascending colon removed by colectomy from a 73-year-old woman proliferated *in vitro* in an organotypic medium and the tumor lived for three years without losing its vitality, its proliferating power, and its structure. The tumor grew on a culture medium consisting of ten parts of Gey's solution containing 1% agar-agar, four parts of foal serum, and four parts of a nine-day-old chicken embryo extract by volume, to which penicillin, fungizone, kanamycin and mesonephros fragments from chick embryos were added. The tumor also grew on the above medium when the mesonephros fragments were substituted either by a mesonephros dialysate, a dialysate of beer yeast, a dialysate from the liver of three- to six-month-old chickens or Tyrode's solution. Five amino acids at high levels of concentration were found to be indispensable for tumor growth; these were all contained in the above media. After three years of growth the explantate was massive, discoid or ovoid and transparent; histologic examination presented an aspect of adenocarcinoma. The RNA and DNA content increased from the ninth to the 13th growth cycle by 220 to 680%. The Gold and Freedman antigen appeared to be generated by the explant throughout the whole observation period.

2823 CARCINOMAS FROM RAT LIVER CELLS TRANSFORMED SPONTANEOUSLY IN CULTURE. (E.) Oshiro,

Y. (Nat'l. Cancer Inst., Bethesda, Md.), L. E. Gerschenson and J. A. DiPaolo. *Cancer Res* 32(4): 877-879, 1972.

Frozen adult Wistar rat liver cells which had previously been in culture for nine months were thawed and reestablished in culture. Before freezing, the cells were nontumorigenic. One month after reestablishment in culture, approximately 50% of the cells had structural chromosomal aberrations. The spontaneously transformed cells had a modal number of 63 chromosomes (stem-line was from 56 to 67). Karyotypic analysis revealed the presence of three new markers (two large metacentrics and one minute chromosome). Injection of more than  $10^7$  cells s.c. into Sprague-Dawley rats which had been previously irradiated with 400 R of X-ray resulted in the development of progressively growing skin carcinomas 3 cm in diameter, within 1 wk. These tumors histologically resembled those resulting from reimplan-

tation of a Reuber hepatoma cultured for 6 months *in vitro*. Morphological and biochemical characteristics of the spontaneously transformed cultured liver cells indicated that they were probably differentiated parenchymal cells.

- 2824 DISSEMINATION OF CANCER CELLS BY NEEDLE BIOPSY OF THE LUNG. (E.) Berger, R. L. (U. Hosp., Boston, Mass.), E. L. Dargan and B. L. Huang. *J Thorac Cardiovasc Surg* 63(3):430-432, 1972.

Two case histories are reported which provide evidence consistent with the dissemination of cancer cells into the pleural space by needle biopsy of the lung. The first case was a 57-yr-old female who was operated upon for a metastatic tumor of the brain and who had an 8-mm coin lesion in the right upper lobe of the lung with no pleural effusion. A needle biopsy under fluoroscopic control was followed by a persistent right-sided hydropneumothorax. A right-sided thoracentesis yielded 500 ml of straw-colored fluid which contained class V tumor cells, similar to those seen in the needle biopsy specimen. The second case was that of a 48-yr-old male with a right upper lobe density and no pleural effusion. After a needle aspiration biopsy under fluoroscopic control, a hydropneumothorax developed. A localized tumor was removed from the right upper lobe after aspiration of the pleural effusion. Both the specimen from the needle biopsy and the aspirated pleural fluid contained similar epidermoid carcinoma cells. Transthoracic needle biopsy is therefore not justified in operable pulmonary malignancies and should be performed only in cases of inoperable lesions.

- 2825 DEFECTIVE FORMATION OF THE LAMELLAR CYTOPLASM BY NEOPLASTIC FIBROBLASTS. (E.)

Domnina, L. V. (Acad. Med. Sci. USSR, Moscow), O. Y. Ivanova, L. B. Margolis, L. V. Olshevskaja, Y. A. Rovensky, J. M. Vasiliev and I. M. Gelfand. *Proc Nat Acad Sci USA* 69(1):248-252, 1972.

A study of the growth pattern of L cells in mixed tissue culture, mouse L cells and untransformed mouse embryo (normal) fibroblasts, and of the possible structural basis of growth is presented. In mixed culture, L cells were able to form colonies above the monolayer of normal fibroblasts. Results obtained by microcinematography suggested the existence of a defective attachment to the substratum by the L cells in mixed cultures. This was further investigated by means of scanning electron microscopy which showed that the mean area of lamellar cytoplasm was three to four times less in L cells than in normal fibroblasts. It is concluded that this deficiency probably is the basis for the L cells' inability to interact normally with the embryo fibroblasts. This phenomenon might be a factor in the mechanisms of invasion and metastasis.

- 2826 <sup>67</sup>GA-ACCUMULATION IN MALIGNANT TUMORS AND IN THE PRELACTATING OR LACTATING BREAST. (E.) Fogh, J. (Dept. Nuclear Med., Copenhagen, Denmark). *Proc Soc Exp Biol Med* 138(3):1086-1090, 1971.

Ninety-two patients with a variety of tumors were given carrier free <sup>67</sup>Ga as a citrate i.v. and scintigrams were made 48-72 hr later to detect <sup>67</sup>Ga accumulation. Of 66 patients with proven malignancies, 59 showed one or more pathological accumulations of <sup>67</sup>Ga in tumor tissue. Only one of 22 benign lesions accumulated detectable <sup>67</sup>Ga. Of special interest was the finding of massive accumulations of <sup>67</sup>Ga in breasts of three women in the puerperal period. Only one of these women had a tumor. <sup>67</sup>Ga was present in milk of one of these patients, but its presence was not thought to be the cause of the intense <sup>67</sup>Ga accumulation in breast tissue. This accumulation was thought to be due to physiological changes in breasts during pregnancy and puerperium.

- 2827 SERUM ENZYMIC ACTIVITY OF L-LACTATE: NAD OXIDOREDUCTASE (LDH) AND ITS VARIANTS IN NORMAL MICE AND IN MICE WITH LEUKAEMIA (L 14 AKR) AND WITH ASCITIC SARCOMA S 180. (E.) Motycka, K. (Inst. Haematology Blood Transfusion, Charles U., Prague, Czechoslovakia), A. Jandova, A. Pezlarova and E. Hermanova. *Neoplasma* 19(1):33-40, 1972.

Lactate dehydrogenase (LDH) activity was determined in sera from normal mice of the inbred AKR strain and noninbred H strain from L 14 leukemia-bearing AKR mice and from ascitic sarcoma S 180-bearing AKR mice by spectrophotometric measurement of the production of NAD<sup>+</sup> from NADH at 340 nm. LDH activities in sera of normal mice exhibited mean values of 450±315 mU/ml in the inbred strain AKR and 474±146 mU/ml in the noninbred strain H. After cellular transplantations of leukemia L 14 AKR and sarcoma S 180, the activities increased five- to sevenfold (2305±1640 and 3025±1077 mU/ml, resp.). To determine whether the elevated serum LDH values in tumor-bearing animals were due to LDH-virus contamination, the S 180 cells were cultivated in tissue culture for six months before injection. Although LDH activity in H strain mice inoculated with S 180 cells withdrawn from tissue culture was slightly greater than that of normal mice, it was considerably lower than that of mice bearing tumor cells passed *in vivo*. Estimation of serum LDH activities on the third to tenth day after injection of L 14 AKR leukemia cells showed that activity increased as the leukemia progressed. Agar-gel electrophoresis of LDH from tumor-bearing mice revealed six bands instead of the five seen in LDH fractions of human sera. Although greatest activity was seen in the sixth band in both normal and tumor-bearing mice, a slight shift to the fifth band was observed in S 180- and advanced L 14 AKR-tumor bearing animals. It is concluded that posttransplantation increases in serum LDH activity are due to contamination



of the inoculates with an LDH virus which can be eliminated by cultivation of tumor cells in tissue culture.

- 2828 A GENETICALLY CAUSED EMBRYONAL ECTODERMAL TUMOR IN THE MOUSE. (E.) Artzt, K. (Cornell U. Med. Coll., New York, N.Y.) and D. Bennett. *J Nat Cancer Inst* 48(1):141-158, 1972.

Female mice derived from line-bred stocks carried in the system  $T\ t^w/t^{w18} \times T\ t^w/t^{w18}$  were used as sources of embryos containing an overgrown primitive streak mass controlled by the  $t^{w18}$  gene. Embryos homozygous for  $t^{w18}$  develop excessive undifferentiated primitive streak material, apparently as a result of a genetic block to differentiation through the primitive streak. To investigate the malignant potential of the overgrown primitive streak mass of homozygous  $t^{w18}/t^{w18}$  embryos, 46 homozygous eight-day embryos were transplanted to testes of adult mice and observed after one month of growth. Fifteen of the homozygous eight-day embryos, when grafted for over 28 days, produced malignant growths, while grafts from normal embryos produced benign teratomas. Malignant growths produced by homozygous embryos resembled a neuroblastoma-medulloblastoma, and showed proliferating and invasive neuroepithelial elements. Fifty-eight seven-day homozygous embryos were also transplanted. Five malignant tumors resulted; these tumors were similar to tumors produced by grafting eight-day embryos. Secondary transplants of tumors could be maintained s.c. on recipients for 35 days without regression by treating recipients of these grafts with anti-thymocyte serum. Secondary transplants differentiated into ectodermal benign tumors. The evidence was thought to support the hypothesis that a gene known to act on the process of differentiation can produce an abnormally differentiated tissue which is at the same time malignant.

- 2829 METABOLIC STUDIES ON MAMMARY TUMOR MTW9 FOLLOWING RESECTION OF THE MAMMOSOMATOTROPIC TUMOR MtTW5. (E.) Biswas, S. (Mount Sinai Sch. Med., New York, N.Y.) and V. P. Hollander. *Cancer Res* 31(10):1360-1363, 1971.

The effect of mammosomatotropic tumor resection on thymidine incorporation and amino acid metabolism in the mammary tumor during regression was observed. The hormone-dependent rat mammary tumor MTW9 and the pituitary tumor MtTW5 were used. Mammary tumor MTW9 does not grow in Wistar-Furth rats unless mammosomatotropic pituitary tumor MtTW5 is also transplanted. Resection of the latter tumor causes prompt regression of the former. Twenty-four and 72 hr after resection of MtTW5, significant increases in DNA concentrations of MTW9 were evident. Incorporation of  $^3\text{H}$ -thymidine into MTW9 acid-insoluble fractions was reduced 24 and 72 hr after resection of MtTW5 by 60 and 84%. Uptake of  $\alpha$ -aminoisobutyric acid, glycine, methionine and possibly phenylalanine into the trichloroacetic acid-insoluble fraction of MTW9 slices was reduced 24 hr after MtTW5 resection. Significant inhibition

in the incorporation of  $^{14}\text{C}$ -glycine (46%),  $^{14}\text{C}$ -methionine (31%) and  $^{14}\text{C}$ -phenylalanine (27%) by MTW9 slices were observed at 24 and 72 hr after resection of MtTW5.

- 2830 STUDIES ON THE MECHANISM OF INHIBITION BY POLYENIC ANTIBIOTICS OF NUCLEIC ACID BIOSYNTHESIS IN ASCITES TUMOR CELLS. (E.) Strom, R. (Inst. Biochem., U. Rome, Italy), A. Bozzi, A. S. Santoro, C. Crifo, B. Mondovi and A. R. Fanelli. *Cancer Res* 32(4):868-876, 1972.

The mechanism by which lucensomycin inhibits DNA and RNA synthesis in Ehrlich and Yoshida ascites tumor cells is studied. In all cases studied lucensomycin (0.8 to 5.6  $\mu\text{g}/10^6$  cells) inhibited  $^3\text{H}$ -uridine and  $^3\text{H}$ -thymidine incorporation into cell material reaching a final value within one minute after addition to the incubation medium. The percentage inhibition did not depend on the concentration of lucensomycin in the medium, but rather on the ratio between the amount of antibiotic and the number of cells. Although uridine and thymidine incorporation into Ehrlich cells showed equal sensitivity to the antibiotic, uridine incorporation into Yoshida cells was less sensitive, possibly due to larger cell size as compared to Ehrlich cells. These results were confirmed by autoradiography. Addition of lucensomycin (1.6 and 3.3  $\mu\text{g}/10^6$  cells) caused an immediate increase of fluorescein efflux from fluorescein-loaded cells which followed first-order kinetics regardless of cell population heterogeneity. Cell permeability to high-molecular-wt compounds (e.g. LDH, M.W., 140,000) also increased with lucensomycin addition. The increase in cell membrane permeability and inhibition of nucleic acid synthesis appeared to be strictly correlated. The N-acetyl derivative of lucensomycin also produced membrane changes but cells were 40 times less sensitive as compared with the parent antibiotic. Incorporation of  $^3\text{H}$ -UTP and  $^3\text{H}$ -TTP by isolated nuclei was unaffected by lucensomycin. Cells treated with antibiotic became permeable to externally added nucleotides, which they could utilize for RNA or DNA synthesis. UMP, but not uridine, in concentrations up to 0.3 mM, could substitute for UTP. It is concluded that lucensomycin acted primarily, if not exclusively, by increasing passive diffusion.

- 2831 HUMAN LYMPHOBLASTOID CELL LINES: II. CYTOGENETIC STUDIES. (E.) Steel, C. M. (Western Gen. Hosp., Edinburgh, Scotland), S. McBeath and M. L. O'Riordan. *J Nat Cancer Inst* 47(6):1203-1214, 1971.

Fourteen human lymphoblastoid cell lines were examined for abnormal karyotypes. Eight lines came from patients aged 13-30 yr with infectious mononucleosis (IM); five lines came from patients aged 11-93 yr with chronic, acute or subacute lymphatic leukemia; and one line came from a 67 yr old patient with atypical myelofibrosis. Four lines from

elderly patients were aneuploid and eight lines from younger IM patients were diploid. Although patients' ages, rather than their diseases, seemed to influence the karyotypes of established cell lines, no clear correlation for either age or disease with karyotype was evident. Observations on two lines, one from an IM patient and one from a chronic lymphatic leukemia patient, indicated that an aneuploid line could evolve *in vitro* from an inoculum of diploid cells. It was also seen that the modal karyotype of a mass culture could change by the emergence of a clone growing more rapidly than the parent line. A marker C-group chromosome with a prominent subterminal constriction of the long arm was seen only in cells from one chronic lymphatic leukemia patient (89% of these cells had the marker chromosome). Other chromosomal aberrations (seen only in leukemia and myelofibrosis patients) included an extra C-group chromosome and an enlarged D-group chromosome. However, there was no evidence for the recurrence of specific aberrations among different cell lines.

- 2832      TRANSFER RNA SPECIES IN SOLID HUMAN TUMORS.  
(E.) Penhoet, E. E. (Dept. Biol., U. California, La Jolla) and J. J. Holland. *J Nat Cancer Inst* 47(6):1173-1177, 1971.

Chromatographic analyses of tRNAs in normal human tissues and various solid human tumors were performed to ascertain whether alterations in tRNAs were involved in spontaneous neoplastic formation. Methylated albumin Kieselguhr (MAK) column and reverse phase chromatographic techniques were employed. tRNAs from all the normal human tissues tested showed similar MAK chromatographic profiles. Aminoacyl tRNAs from all tumors tested had identical properties to those seen in normal human liver tissue, with one exception; one of three breast carcinoma biopsy specimens contained a tyrosyl tRNA population with noticeably different chromatographic features than those of other tumors or normal human tissues. This sample had considerable tRNA eluting from both MAK and reverse phase columns at a higher salt concentration, than most of the normal liver tyrosyl tRNA. This tyrosyl tRNA was chromatographically similar to that found in cultured HeLa cells. These results suggest that alterations in tRNA do occur in some human tumors but are not obligatory in human cell tumorigenesis.

- 2833      THE EFFECT OF INDUCED DIABETES ON EXPERIMENTAL TUMOR GROWTH IN MICE. (E.)  
Puckett, C. L. (Duke U. Med. Ctr., Durham, North Carolina) and W. W. Shingleton. *Cancer Res* 32(4): 789-790, 1972.

The effects of induced diabetes and the attendant hyperglycemia on the growth of an experimental malignant neoplasm in mice were studied. Four groups of female C3H mice were established: 1) 24 mice made diabetic by a single i.p. injection of

300 mg/kg of alloxan and one week later given a mammary carcinoma transplantation in the axillary fold; 2) 24 normal mice given tumor transplants at the same site as the preceding group; 3) five normal mice receiving no treatment at all, and 4) five diabetic mice receiving no tumor transplant. All of the mice given tumor transplants were sacrificed at the end of three weeks. The mean tumor weight in the control tumor group was 1.84 g while in the diabetic group the mean tumor weight was 0.78 g. Crude volume determinations showed a mean mass of 2.49 ml in the control group and 1.12 ml in the diabetic group of mice. Since the diabetic tumors attained an ultimate size and weight approximately one-half of that of the control group, the diabetes in this study model apparently retarded tumor growth.

- 2834      CARCINOMA OF THE BREAST AND KLINEFELTER'S SYNDROME. (E.) Harnden, D. G. (U. Birmingham, England), N. Maclean and A. O. Langlands. *J Med Genet* 8(4):460-461, 1971.

Examination of sections of tumor tissue, buccal smears, cultured leukocytes or skin fibroblasts revealed the presence of sex chromatin in five of 150 cases of carcinoma of the breast in males. Three cases were confirmed to have an XXY sex chromosome constitution and the clinical histories from the remaining two cases (the patients were already deceased) were compatible with such a composition. Two of the cases were confirmed histologically and clinically to be Klinefelter's syndrome. These data show a frequency of 33.3 chromatin-positive cases per 1000 males with breast cancer, a highly significant increase over the frequency of 1.9 per 1000 in newborn males.

- 2835      L2C GUINEA PIG LYMPHATIC LEUKEMIA: A "B" CELL LEUKEMIA. (E.) Shevach, E. M. (Natl. Inst. Allergy Infect. Dis., Bethesda, Md.), L. Ellman, J. M. Davie and I. Green. *Blood* 39(1):1-12, 1972.

Methods for determining whether cells are derived from bone marrow (B) cells which are responsible for antibody production or thymus (T) cells which are responsible for cell-mediated immunity were applied to the study of L2C guinea pig lymphatic leukemia. It was shown by immunofluorescent studies, by detection of lymphocyte complement receptor for antigen-antibody complement complexes on L2C and lymph node cells, by rosette formation with antigen-antibody-mouse complexes, and by failure to respond to several common mitogens capable of stimulating thymus-derived lymphocytes, that L2C guinea pig lymphatic leukemia is a B cell leukemia. Experimental results also indicated that L2C leukemia may be useful in producing specific anti-guinea pig T cell and anti-guinea pig B cell antisera. Thus, applications of these techniques to classify human leukemias may prove of future theoretic and therapeutic value.



- 2836 SERUM HISTAMINASE AND CALCITONIN LEVELS IN MEDULLARY CARCINOMA OF THE THYROID. (E.) Baylin, S. B. (Natl. Inst. Hlth, Bethesda, Md.), M. A. Beaven, H. R. Keiser, A. H. Tashjian, Jr. and K. E. W. Melvin. *Lancet* 1(7748):455-458, 1972.

Serum-histaminase activity, as determined by breakdown  $\beta$ - $^3\text{H}$ -histamine to  $^3\text{H}_2\text{O}$ , and calcitonin levels, as determined by radioimmunoassay, were measured in 62 healthy males and females and in 42 patients with localized or metastatic medullary carcinoma of the thyroid, 33 of whom were members of three families in which the disease was inherited. Whereas histaminase activity in controls averaged 1.6 U/ml 50% of the patients with carcinomas had values greater than 3.5 U/ml. Twenty-six other members of two of the families with a history of thyroid carcinoma, who did not have the disease, were tested and shown to have normal histaminase activity. Of the 26 patients with metastatic tumor, eight had high enzyme activity ( $>3.5$  U/ml), with the highest activity in patients with pulmonary metastases. Serum-histaminase activity fell after removal of neck tumor in 14 of 20 patients, but did not fall to normal levels in the other six patients, four of whom had evidence of metastatic tumor. Basal serum-calcitonin levels were above normal ( $>0.38$  ng/ml) in 29 of 31 patients with medullary thyroid carcinoma. Calcitonin fell to low or undetectable levels in 17 of the 20 patients who had neck tumors removed. These results suggest that although measurements of serum-histaminase activity may be useful in the search for metastases and the detection of residual tumor after surgery, measurement of basal serum-calcitonin levels is probably a more reliable test for the early detection of localized medullary thyroid tumor.

- 2837 BACTERIA AS CELL SURFACE MARKERS ON NORMAL AND MALIGNANT MAMMALIAN CELLS. (E.) Meadows, P. S. (Dept. Zoology, U. Glasgow, Scotland). *Experientia* 27(11):1321-1322, 1971.

The microtopography of the cell surfaces of cultured WI38 human embryonic lung fibroblasts and HeLa cells were studied by photomicrographic measurement of differences in the absorption of *Aeromonas liquifaciens*, *Escherichia coli* and *Pseudomonas fluorescens* to the surface membranes. Within 15-20 min more bacteria were attached to the cells than to the glass between the cells, and the ratio was higher for the HeLa (malignant) cells than for the normal WI38 cells. The bacteria on the cells were aggregated and there were more aggregates on the HeLa cells, especially on cells which were not in contact with other cells. On both HeLa and WI38 cells, aggregates were more commonly found at or near the leading edge of the cell or at both ends of a bipolar shaped cell. Aggregates on HeLa cells were most often seen on areas of the cell surface close to the nucleus. It is suggested that these different patterns of adhesion may be relevant to cell locomotion and to surface difference between malignant and normal cells.

- 2838 PATHOLOGIC, MORPHOLOGIC AND CYTOLOGIC CHARACTERISTICS OF SPONTANEOUS MAMMARY GLAND TUMORS IN MICE SUBJECTED TO LONG TERM ADMINISTRATION OF HOMOLOGOUS RNA. (Rus.) Ronichevskaya, G. M. (Acad. Med. U.S.S.R., Novosibirsk), N. A. Matienko and R. P. Martynova. *Vop Onkol* 17(6):62-66, 1971.

The dynamics of morphologic and cytogenetic alterations in spontaneous mouse tumor tissue were studied following administration of RNA preparations from a low tumor strain of mice. Female A and C3H mice with mammary gland tumors were treated with RNA (3 mg/mouse, s.c. twice daily for 1-3 months) from liver, kidney, spleen and lymph node tissues of C57Bl mice. Twenty days after the beginning of the experiment mitotic inhibition appeared to be almost total in the neoplastic tissue of the treated animals. Degenerative processes, including nuclear hypersegmentation, decreasing cytoplasm volume, cell shrinkage and nuclear pyknosis were observed 30-40 days after the beginning of treatment. Necrotic processes were seen in the core region of the tumor and were sometimes associated with the formation of small abscess foci. Of the treated animals, 6.9% developed a connective tissue scar on the site of the adenocarcinoma; none of the 143 control mice showed similar phenomena. Neoplasms of the control animals exhibited 7.3% polynuclear cells throughout the experimental period, while those of the treated mice varied between 10.5 to 15.6%. A considerable decrease in metastases was observed in treated animals when compared to control mice. However, no sufficient evidence as to the inhibitory action of homologous RNA in the synthesis of tumor tissue RNA could be obtained.

- 2839 SYNTHESIS AND RELEASE OF HUMAN GROWTH HORMONE FROM LUNG CARCINOMA IN CELL CULTURE. (E.) Greenberg, P. B. (Royal Melbourne Austin Hosp., Australia), T. J. Martin, C. Beck and H. G. Burger. *Lancet* (7746):350-352, 1972.

Cells obtained from a poorly differentiated lung carcinoma of a 73-yr-old female with hypertrophic pulmonary osteoarthropathy were maintained in culture for four months. Synthesis of human growth hormone (HGH) *in vitro* was demonstrated by the incorporation of label from  $^{14}\text{C}$ -leucine into material with the characteristics of HGH on Sephadex G 100 gel filtration and paper chromatography. Release of immunoreactive human growth hormone (IRHGH) from the cultured cells was stimulated by theophylline (2 mM) and dibutyryl cyclic- $3'5'$ -adenosine monophosphate (1 mM). Preoperatively, the patient had a diabetic glucose tolerance and high fasting levels of plasma IRHGH, both of which returned to normal after resection of the lung tumor. The tumor contained a higher IRHGH concentration (190 ng/g) than did the adjacent lung (60 ng/g). IRHGH was released into the medium surrounding the cultured tumor cells at a concentration of 3-13 ng/ml. Serial dilutions of these samples inhibited the binding of  $^{125}\text{I}$ -labeled HGH specific antibody in a manner similar to that produced by the HGH standards. These findings

are consistent with synthesis and release of HGH by the carcinoma *in vivo*.

- 2840 CANCER OF THE CERVICAL STUMP: A STUDY OF 173 PATIENTS. (E.) Wolff, J. P. (Gustave Roussy Cancer Inst., Villjuif, France), J. Lacour, D. Chassagne and M. Berend. *Obstet Gynec* 39(1):10-16, 1972.

Three aspects of cancer of the cervical stump are considered: 1) a comparison of the features of this cancer with those of cancer of the cervix in general; 2) the clinical types of cervical stump cancer and their development; and 3) its treatment. Pathologic findings indicated that of 173 patients treated for this disease during an 11-yr period, 44% had squamous cell epithelioma; 36%, intermediate squamous cell epithelioma; 8%, adenocarcinoma, and 10% were listed as undifferentiated epithelioma, with the remaining 2% having no histologic diagnosis available. Cancer of the cervical stump was of two types, one "left behind" after subtotal hysterectomy and the other arising *de novo* from the stump itself. An interval of two yr or less occurred between subtotal hysterectomy and subsequent malignancy in 42 of the cases, which probably represented the first type. Survival rate was significantly lower in this group than in the group in which an interval of more than two yr occurred between the surgical procedure and appearance of the malignancy. Treatment of the patients which is the same as that for cervical cancer, is discussed in light of the incidence, delay in appearance of subsequent lesion, response to treatment of local recurrence and frequency of metastases. The findings reported are interpreted as indicators for discontinuance of subtotal hysterectomy in favor of total removal because of potential dangers to a patient's future.

- 2841 THE ACUTE LEUKEMIC CELL: V. RNA SYNTHESIS IN PERIPHERAL BLOOD AND BONE MARROW. (E.) Schumacher, H. R. (Harrisburg Hosp., Pa.), A. E. McFeely, K. D. Davis and T. K. Mangel. *Amer J Med Sci* 262(6):327-332, 1971.

RNA synthesis in bone marrow and peripheral blood cells from nine leukemic and 20 normal individuals was determined by autoradiographic and liquid scintillation analysis of <sup>3</sup>H-uridine incorporation *in vitro*. RNA synthesis in bone marrow blasts appeared to be about the same in both normal and leukemic subjects, although the total percentage of cells labeled in leukemic patients was greater in both bone marrow and peripheral blood than in normal subjects. Although marrow and peripheral blood RNA synthesis did not appear to be related, synthesis was greater in the marrow than in the peripheral blood of both groups. It is concluded from this that only these cells which have decreased or stopped RNA synthesis are released by the marrow into the peripheral blood. These cells are thought to represent the more mature elements with greater cellular elasticity. The difference

between immature and mature blasts was further emphasized by the finding that large leukemic blasts (immature) in both marrow and peripheral blood incorporated more <sup>3</sup>H-uridine than did small blasts (mature).

- 2842 GROWTH RATE OF PULMONARY METASTASES FROM OSTEOSARCOMAS. (Rus.) Marmorshtein, S. Ya. (P. A. Gertsen Sci. Res. Inst. Oncol., Moscow, USSR), P. E. Kunin, L. S. Zvekotkina, I. P. Kuznetsova and V. P. Karp. *Vop Onkol* 17(9):42-47, 1971.

Estimation of the tumor doubling time for 46 pulmonary metastases in 17 patients with osteosarcomas showed that the mean doubling rate was 34±5 days in 13 patients (37 metastases) and 155±32 days in 4 patients (9 metastases). The difference between the mean doubling time in these two groups of patients is statistically significant. A comparison of radiological findings with the onset of clinical symptoms suggests that in patients with the more rapidly developing metastases, the metastases develop at about the same time as the primary tumors. The slower growth rate of metastases in the second group may be due to a more "benign" course of the primary tumor, possibly as a response to chemotherapy or perfusion, or to interactions between the tumor and the organism.

- 2843 DIFFERENCE IN THE CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE LEVELS IN NORMAL AND TRANSFORMED CELLS. (E.) Sheppard, J. R. (U. Colorado Med. Sch., Denver). *Nature New Biol* 236(61):14-16, 1972.

Steady-state cyclic 3'5'-adenosine monophosphate (cAMP) levels in normal and transformed cells were determined by an *in vitro* assay, and the effect of several biochemicals on these levels was studied. These cAMP levels were at least two times higher in normal density-dependent (3T3) cells as compared with virus-transformed (py 3T3) and spontaneously transformed (3T6) cells. Pollack's flat revertants (fLSV and flpy), which exhibit normal growth, had levels of cAMP in the range of normal 3T3 cells. When cAMP levels in 3T3, 3T6 and py3T3 cells were studied over a seven-day growth period, little change was seen as the cells reached confluency, indicating that cAMP levels in these cells were not affected by their state of growth. When insulin, 50% calf serum or 0.05% trypsin, which have been shown to stimulate confluent normal cells to further growth, were added to confluent 3T3, 3T6 or py3T3 cultures, cAMP levels were depressed two- to threefold within five min. Prostaglandin E<sub>1</sub>, which may inhibit cellular growth in virally and spontaneously transformed cells, increased cAMP levels within five min; the extent of stimulation was greater (sixfold) in the 3T3 cells, as compared with the transformed 3T6 and py3T3 cells (twofold). cAMP levels had returned to basal values by three hr. Prostaglandin F<sub>2α</sub> had no effect on cAMP levels in 3T3, 3T6 or py3T3 cells. These results are consistent with the hypothesis that cAMP plays a role in the control of cellular growth.



- 2844 MEMBRANE CHANGES ASSOCIATED WITH MALIGNANCY. (E.) Inbar, M. (Weizmann Inst. Sci., Rehovot Israel), H. Ben-Bassat and L. Sachs. *Nature New Biol* 236(61):3-4, 1972.

Cell agglutination and membrane binding to isotopically labeled concanavalin A (con A) were studied *in vitro* in normal and virus-transformed hamster and mouse (3T3) cells and were related to the tumorigenicity of the cells *in vivo*. Polyoma-, SV40- and dimethyl-nitrosamine-transformed hamster cells were not agglutinated by con A until day 2 after seeding, after they had undergone one cell generation, and they reached maximum agglutinability on day 4. Transformed cells grown under conditions which enhanced cell replication were agglutinated even after one day of subculture. Inhibition of replication of the transformed cells by low temperature or by 5-fluorodeoxyuridine prevented agglutinability, but once they had gained agglutinability, inhibition of replication did not reverse that property. Normal cells were not agglutinated by con A even when cell replication was enhanced. Although a similar number of  $^{63}\text{Ni}$ - or  $^3\text{H}$ -con A molecules was bound per transformed cell at days 1 and 4 after subculture, cell surface area had decreased by 50% during the same time period, indicating that exposed con A binding sites had been concentrated. The number of palpable tumors resulting from s.c. injection into adult hamsters of dissociated non-agglutinating and agglutinating transformed hamster cells increased as cells were subcultured during days 1-4 and were greater in the more agglutinable cell lines. Non-agglutinating transformed cells became agglutinable and more tumorigenic after treatment with trypsin. Although trypsin-treated normal cells became agglutinable, they did not produce tumors. Transformed 3T3 cells were agglutinated by soybean and wheat germ agglutinin, but not by con A at day 1, whereas they were agglutinated by all three substances at day 4. The association between an increase in agglutinability and malignancy was specific for con A, no such correlation being found for wheat germ or soybean agglutinins. The acquisition of malignancy thus presumably requires a change in location of con A binding sites and an activation of con A-specific metabolic activity on the surface membrane.

- 2845 HISTOCHEMICAL EVIDENCE OF CELL DEATH IN TRANSPLANTED TUMOURS. (E.) Sylven, B. (Karolinska Inst., Stockholm, Sweden) and M. Niemi. *Virchows Arch Abt B Zellpath* 10(2):127-133, 1972.

Unicentric transplants of fibrosarcomas, MCIS rhabdomyosarcomas, ELD hypotetraploid carcinomas and mammary carcinomas in non-conditioned C3H X F<sub>1</sub> hybrid mice were examined histochemically for evidence of tumor cell death. They were stained for lysosomal leucyl naphthylamidase (LDase) activity at pH 5.5, an indication of the presence of autolytic vacuoles. All tumor types presented the same general appearance and LDase patterns. Viable, growing, peripheral tumor cells, as well as normal growing fibroblasts and epithelial cells, contained a few distinct LNase-

positive "lysosome-like" granules, indicating that LDase activity was a regular characteristic of both cell types. The tumor periphery also contained occasional irregularly scattered tumor cells with large, autolytic, strongly LDase-positive, vacuoles. Similar foci of these cells were seen at about 50  $\mu$  from the tumor periphery and were assumed to represent the first sites of incipient tumor necrosis. Near the tumor centers and, especially, adjacent to necrotic areas were large numbers of similar tumor cells with greatly enlarged, LNase-positive autophagosomes. It is concluded from this latter observation that the peripheral tumor cells with autolytic, LDase-positive vacuoles are destined to die and that this change represents an early sign of impending degeneration. Typical B-type tumor cells representing viable but non-growing parts of the population are mostly devoid of LDase-positive organelles. The LDase histochemical method might thus prove useful in estimating accelerated tumor cell death after irradiation or chemotherapy.

- 2846 ELEVATED ACTIVITY OF OLIGOMYCIN-SENSITIVE ATPase IN LYMPHOCYTES FROM PATIENTS WITH LUNG CARCINOMA. (E.) Ellegaard, J. (Hahnemann Med. Coll. Philadelphia, Pa.) and N. V. Dimitrov. *Proc Soc Exp Biol Med* 139(3):734-737, 1972.

ATPase activity was determined and characterized in homogenates of purified peripheral blood lymphocytes from 12 patients with lung carcinoma and compared with that of lymphocytes from 22 normal patients and from ten patients with nonmalignant diseases. Enzyme activity in lung cancer patients was significantly higher (10  $\mu$ moles P<sub>i</sub> liberated/mg protein/30 min) than that of either of the other two groups (0.3  $\mu$ mole P<sub>i</sub> liberated/mg protein/30 min). Addition of ouabain (0.5mM) to, or omission of Na and K from, the reaction mixture had no effect on enzyme activity. Addition of oligomycin (20  $\mu$ g/ml) considerably decreased activity and addition of 2,4-dinitro-phenol (0.1 mM) increased enzyme activity. Addition of sodium fluoride (10 mM) or replacement of MgCl<sub>2</sub> totally inhibited activity.

- 2847 AN ABNORMAL CELL-LINE IN A PATIENT WITH ACUTE GRANULOCYTIC LEUKEMIA: CYTOGENETIC STUDIES BEFORE AND AFTER AN ALLOGENEIC MARROW TRANSPLANT. (E.) Littlefield, L. G. (Med. Div., Oak Ridge Assoc. U., Tenn.). *Cancer* 29(5):1281-1286, 1972.

Cytogenic studies of the marker stem-line are presented. Tests are completed on bone marrow aspirate and peripheral blood both before and after a bone marrow transplant acquired from a 52-year-old patient with granulocytic leukemia. Well-stained and well-spread metaphases were selected for study. Pretransplant evaluation of marrow preparations indicated that 91% of the 24 metaphases were abnormal. All aberrant cells were hypodiploid, having a modal number of 45 chromosomes and consistent rearrangement, involving the

group D and G chromosomes. Hematologic studies at this time showed a leukemic marrow with 17% blasts. Although post-marrow transplants were highly acellular, eight metaphase groups could be analyzed, four of which had normal 46XY chromosome complements. The remaining four had counts of 43, 43, 44 and 45, and each contained seven large acrocentric chromosomes. Cytogenic preparations were made from aspirate specimens drawn on the 8th, 26th, 44th and 68th day after transplant. No cells with definite marker aberrations were seen. Cytogenic studies using markers are recommended as useful tools in determining a "take" in marrow graft transplantation, since they provide continuous monitoring of patient condition and permit determination of the establishment of the graft itself.

- 2848 STRUCTURAL ANALYSIS OF NUCLEOLAR PRECURSORS OF RIBOSOMAL RIBONUCLEIC ACIDS: SEQUENCE ANALYSIS OF LONG OLIGONUCLEOTIDES PRODUCED BY T<sub>1</sub> RIBONUCLEASE DIGESTION OF NUCLEOLAR AND RIBOSOMAL 28S RIBONUCLEIC ACID OF NOVIKOFF HEPATOMA ASCITES CELLS. (E.) Inagaki, A. (Baylor Coll. Med., Houston, Texas) and H. Busch. *J Biol Chem* 247(10):3327-3335, 1972.

Complete T<sub>1</sub> RNase digestion was carried out on purified, isotopically labeled, nucleolar precursor and ribosomal 28S RNA of Novikoff ascites tumor cells which were preincubated *in vitro* (six and 18 hr, resp.) with <sup>32</sup>P-orthophosphate. Two large fragments, with chain lengths of 28 (δ fragment) and 20 (β fragment) nucleotides, were isolated in highly purified form from digests of both nucleolar precursor and ribosomal 28S RNA by successive chromatography on DEAE-Sephadex at pH 7.5 and DEAE-Sephadex at pH 3.3. The δ fragment was the largest fragment produced by T<sub>1</sub> RNase from the 28S RNA. An examination by two-dimensional electrophoresis of partial digestion of the β fragment indicated that it contained an alkali-stable dinucleotide C<sub>m</sub>-Up. Sequence studies were carried out on δ and β fragments after complete and partial pancreatic RNase digestion, U2 RNase digestion, and partial spleen phosphodiesterase digestion. The sequences of A-A-C-C-U-A-U-C-U-U-C-A-U-C-U-C-A-A-C-U-U-U-A-A-A-U-G for the δ fragment and A-A-A-U-A-C-C-A-C<sub>m</sub>-U-A-C-U-U-C-C-A-U-C-G for the β fragment were the longest obtained for either ribosomal 28S RNA or nucleolar precursor 28S RNA. The sequences of these two large fragments were identical for nucleolar and ribosomal 28S RNA and provided further chemical evidence for the nucleolar origin of ribosomal 28S RNA.

- 2849 HEMOSTATIC ACTIVITIES OF LEUKEMIC CELLS. (E.) Lisiewicz, J. (Hosp. Tortona, Italy), G. Astaldi, J. Okulski and R. Merolla. *Cancro* 23(5): 259-266, 1970.

Thromboplastic and antiheparin activities in eosinophils isolated from the peripheral blood of one patient with eosinophilic reticulosis, lymphocytes from 20 patients with chronic lymphocytic leukemia

(CLL), granulocytes from 20 patients with chronic granulocytic leukemia (CGL), and blast cells from six patients with acute leukemia (AL) were compared with those of blood cells from 20 normal persons. Thromboplastic activity, as determined by *in vitro* plasma recalcification time and the thromboplastin and thrombin generation tests, was present in leukocyte extracts and was greater in extracts of eosinophils, lymphocytes and myeloblasts of leukemic patients than in those of granulocytes from GLC patients and normal subjects. Activity was generally greatest in eosinophil extracts. Although antiheparin activity was observed in all extracts, plasma thrombin time being used as an index, it was greatest in normal leukocytes and in leukemic granulocytes and lymphocytes. It is concluded that since platelet counts are normally low in most leukemia patients, thromboplastin activity in these cases may be due to leukocytes, which may also contribute significant antiheparin activity.

- 2850 CYTOCHEMISTRY OF LEUKOCYTES IN MALIGNANCY. (E.) Jansa, P. (Med. Sch., Purkyne U. Brno, Czechoslovakia) and F. Papousek. *Folia Haemat* 96(1):34-42, 1971.

Pretherapy peripheral blood samples were analyzed from 40 patients, aged 21 to 87 yr, having a variety of advanced carcinomas with metastases. The following cytochemical reactions were tested: PAS, methyl green and pyronine staining alkaline phosphatase, acid phosphatase, non-specific esterase, non-specific naphthol-AS D-chloracetate esterase, peroxidase, succinic dehydrogenase, lactic acid dehydrogenase, α-glycerophosphatase dehydrogenase and DPNH and TPNH diaphorase. No malignant cells were identified in the blood samples in any of the cases but one. Differential white cell counts showed neutrophilia with a relative decrease in lymphocytes, as compared with blood from normal control subjects. A population of abnormal monocytes comprised from 1 to 6% of circulating cells of patients with malignancies. These two forms were distinguished on the basis of morphology and cytochemistry. Although cytochemical results were variable, there did not appear to be a significant difference between atypical cells and cells from normal subjects. These "atypical" cells were, therefore, considered benign.

- 2851 LEUCOCYTE ALKALINE PHOSPHATASES IN LYMPHOMA PATIENTS. (E.) Humphries, K. R. (Wellington Hosp., New Zealand). *N Z Med J* 72(463):389-393, 1972.

Evaluation of serial leukocyte alkaline phosphatase (LAP) scores of 16 malignant lymphoma patients at the Wellington (New Zealand) Hospital radiotherapy clinic was performed from October 1968 to July 1970. LAP scoring was valuable for detection of deterioration in six of nine cases with active disease. On the basis of clinical studies the course of disease in ten of 16 inactive cases of lymphoma could be predicted;



these findings were directly related to low LAP score. It was found that leukocytosis generally produced a corresponding increase in the LAP; the LAP score has also been found to increase in pregnancy. Radiation or chemotherapy, including steroids, did not affect LAP scores unless leucopenia was produced. It is thought that LAP scoring is a rather simple technique for measuring disease activity in lymphoma patients and may be more sensitive for detecting remission or exacerbation than other methods employed.

2852 EXPERIMENTS WITH FLUORESCENT CHROMOSOME STAINING IN BURKITT TUMORS. (E.)

Manolov, G. (Inst. Genetics, U. Lund, Sweden), Y. Manolova, A. Levan and G. Klein. *Hereditas* 68(2): 235-244, 1971.

Fluorescent staining with quinacrine dihydrochloride dye of chromosomes from Burkitt lymphomas of ten patients and from leukocyte cultures from normal subjects was compared to gross chromosome morphology as determined by orcein staining and  $^3\text{H}$ -thymidine incorporation. The banding patterns of chromosomes from lymphoma and normal patients were generally the same, but they were useful in studying marker chromosomes. In one particular case, two long (mar 1 and mar 2) and one medium length telocentric (mar 3) marker chromosomes were observed. The sum of the lengths of mar 1, mar 2 and the one No. 1 and two No. 2 A-group chromosomes was the same as the total lengths of A group chromosomes from a normal patient, suggesting that the markers were formed of missing A group chromosomes. Fluorescence banding analysis showed that mar 1 was primarily derived from the No. 1 group A chromosome. The source of part of the long arm of mar 1 could not be determined. Mar 2 was derived from the No. 3 group A chromosome. Mar 3 represented the short arm of the No. 3 A chromosome. The fluorescence which is normally strong in the distal portion of the long arm of the Y chromosome was shorter and weaker in two of the male tumors.

2853 THE EFFECT OF THE CARCINOGENESIS AND THE PRESENCE OF NEOPLASTIC CELLS ON THE MITOTIC ACTIVITY OF ORAL EPITHELIA IN RATS AND MICE.

(E.) Matsuki, K. (Yamaguchi U. Sch. Med., Japan). *Bull Yamaguchi Med Sch* 17(1-2):53-69, 1970.

Seventy male and female Wister rats were fed a diet containing the carcinogen p-dimethyl-aminoazo-benzene (DAB). Thirty rats received weekly i.m. injections of anabolic steroid hormone which stimulates buccal mucosal and tongue epithelial cells to undergo mitosis, and the other 40 (not injected) rats were used as controls. Cell samples were taken once every 30 days six hr after s.c. colchicine injection. All animals were sacrificed after 150 days and the livers examined. In a similar experiment adult male dd strain mice were injected i.p. with Ehrlich ascites tumor cells and the effect of anabolic steroid hormone on tongue epithelium and

tumor cells was observed. Male rats generally had a higher mortality than female rats. Male rats receiving hormone had a lower incidence of hepatoma than controls; no hepatomas were observed in female rats. In the control group mitotic rates were lower in buccal mucosa of rats with hepatoma than in non-tumor-bearing rats fed DAB for 90 days. The mitotic values of rats treated with hormone were comparable to those of the controls. Mitotic activity in female rats gradually decreased, starting 30 days after DAB feeding began. Mitotic activity of tongue epithelium in tumor-bearing mice showed a slight increase on day seven postinfection followed by a gradual decrease which reached 56% of control on day 16. Mitotic rates of approximately 170% of control rats were observed on these days in hormone-treated rats.

2854 PRIMARY OVARIAN NEOPLASMS IN INFANTS AND CHILDREN: A STUDY OF 81 CASES DIAGNOSED IN FINLAND AND SWEDEN. (E.) Lindfors, O. (Childrens Hosp., U. Helsinki, Finland). *Ann Chir Gynaecol Fenn* 60:12-26, 1971.

Published data on the incidence of ovarian neoplasms in children are briefly reviewed, and results from a study of ovarian neoplasms in children aged three days to 14 yr in Finland and Sweden are presented. The mean annual incidence for 100,000 girls in Helsinki over a 12-yr period was 2.6 ovarian neoplasms and 0.7 malignancies. Of 46 cases of ovarian neoplasms randomly sampled from Finnish and Swedish girls, 20 were found to be malignant. Over a ten-yr period 1.3 out of 24,000 patients/year were seen with an ovarian neoplasm in the outpatient department of Aurora Hospital, Helsinki. Mortality from ovarian malignancy based on figures from Helsinki was 0.6/100,000. It was concluded that the incidence of, and mortality from, ovarian neoplasms in children were quite low. Incidence of both benign and malignant ovarian neoplasms increased gradually with age up to a maximum at menarche. Of the 81 cases studied, 60 were classified histologically as germ cell tumors, ten as epithelial, eight as granulosa, two as common mesenchymal and one was undefined. The proportion of germ cell tumors was larger at ages 10-14 than younger ages, but smaller than at ages over 14 yr.

2855 STUDIES CORRELATING THE GROWTH RATE OF A TUMOR AND ITS METASTASES AND PROVIDING EVIDENCE FOR TUMOR-RELATED SYSTEMIC GROWTH-RETARDING FACTORS. (E.) DeWys, W. D. (U. Rochester Sch. Med. Dent., N.Y.). *Cancer Res* 32(2):374-379, 1972.

Studies were conducted on the growth of Lewis lung carcinoma in C57BL/6 male mice to determine the effect of local and systemic factors on tumor growth rate. A transplantation of  $2 \times 10^5$  tumor cells was made into the right hind leg muscles. The subsequent growth rate of the primary tumor was followed by serial tumor diameter measurements, and the growth rates of lung and kidney metastases were followed by serial

transplant bioassay. Synchronous slowing of the rate of growth of the implanted tumor and its metastases was observed. Early after transplantation, the implanted tumor grew exponentially, and early lung metastases grew exponentially at a similar rate. Although the early rate of increase in the kidney was slower than the early rates in the other sites, a comparable growth rate in all three locations was observed during the late stages of tumor growth. This similarity implicated systemic growth factors in the regulation of tumor growth rate. To evaluate host immunological reactivity as a systemic factor, groups of mice were challenged with graded numbers of tumor cells, but no experimental group showed an increase in immunological response. Synchronous slowing was also seen in experiments in which metastases were simulated by a second implant. Following removal of the primary tumor, this slowing of tumor growth was reversible in both the lung metastases and the simulated metastases. The degree of inhibition was proportional to length of time the initial tumor was present. In studying the effects of a secondary tumor on the growth rate of a primary tumor, it was found that in groups receiving a second inoculum, the weight of the initial tumor slowed after the second tumor reached detectable size. However, since the sum of the weights in double-tumor groups closely approximated the weight of the tumor in single-tumor groups, it was suggested that the total body burden of tumor, rather than the size of the local tumor, is the determinant of tumor growth rate.

2856 GRANULOCYTE ALKALINE PHOSPHATASE ACTIVITY IN HODGKIN'S DISEASE. (E.) Bobory, J. (U. Med. Sch., Debrecen, Hungary). *Acta Med Acad Sci Hung* 28(1):1-5, 1971.

Granulocytic alkaline phosphatase (GAP) activity was studied histochemically in blood smears obtained from 20 patients with histologically verified Hodgkin's disease. GAP activity was correlated with the stage of the disease (classified in four stages, according to Peters) and an attempt was made to determine whether or not a close relationship existed between changes in GAP activity and relapse. All patients were treated with irradiation or cytostatic drugs. Full clinical remission was associated with normal GAP values in seven of eight patients. The one patient with the high GAP value suffered a relapse one yr later. Increases in GAP activity were associated with recurrences and were also related to the severity of the clinical condition. GAP levels were highest in stage IV patients. Normal GAP values were hardly ever found in stage III or IV patients, even during relative remissions. Parallel increases in GAP activity and in BSR were seen during periods of clinical deterioration. No correlation between GAP changes and changes in RBC or WBC counts was observed. Since many patients failed to present themselves for evaluation during periods of remission, a valid conclusion regarding a relationship between GAP activity and relapse could not be reached.

2857 MYCOPLASMAS (PPLO) AND HUMAN NEOPLASMS. (E.) Niwayama, G. (Sch. Med. U. California, Los Angeles) and J. T. Grace, Jr. *Tohoku J Exp Med* 105(3):257-280, 1971.

This study presents data on the frequency of mycoplasmas (PPLO) from solid neoplasms, leukemic and lymphoma specimens. One thousand five hundred and twenty-five malignant and 19 nonmalignant tissues obtained from surgical procedures and autopsies performed under aseptic conditions were individually homogenized and 2 or 3 drops of the homogenate were inoculated into semi-solid Red V media. Serial weekly passages of 0.5 to 1.0 ml of this medium into semi-solid Red V media were completed and the samples were aerobically and anaerobically incubated. The solid media plates were examined for growth one week after inoculation and were not considered negative until after three to four wk of incubation. Simultaneously, minced tissues were placed in tissue culture medium for viability assay. Results indicated that among specimens classified as leukemia, malignant lymphoma, and multiple myeloma, no direct mycoplasma isolations were encountered. Experimental tissue derived from carcinomas and sarcomas were negative for mycoplasma with the exception of tissue inoculum prepared from a squamous cell carcinoma of the floor of the mouth. No direct isolation of mycoplasma was derived from the control samples. Despite apparent failure of direct isolation of mycoplasma, subsequent studies of the same tissue samples propagated as tissue cultures were successful to a limited degree. Further investigation to determine the nature and relationship of mycoplasma to leukemia and other malignancies is recommended.

2858 THE HISTOCHEMICAL MEASUREMENTS OF THE LIPID CONTENT OF THE PINEAL GLAND IN RATS SUFFERING FROM MALIGNANCY. (E.) Huxley, M. (U. Hosp. South Manchester, England) and E. Tapp. *Brain Res* 37(1):123-125, 1972.

An experiment designed to measure pineal activity through lipid content is presented. Fibrosarcomas are induced in 17 Sprague-Dawley rats by s.c. injection of 2 mg of 9:10 dimethyl-1:2 benzantracene in 0.2 ml arachis oil. Control rats received oil only. When tumors reached 6 cm in diameter rats were killed, pineal gland removed and subjected to controlled chromatin before being imbedded in paraffin. Sections cut at 5  $\mu$ m were stained with Sudan Black B. Lipid content was quantitated by determining the number of lipid spots visualized microscopically in a section of pineal tissue, using a specially calibrated eyepiece. Results showed that the lipid content of the pineal glands of both male and female tumor bearing rats was significantly higher than in the control group. The possible variation factors such as age, sex diurnal activity and estrous cycle were carefully avoided during testing. Recommendation is made for using pineal gland lipid content as a parameter for its secretory activity.



- 2859 FAMILY CANCERS AMONG CASES OF PRIMARY LIVER CANCER. (E.) Hagstrom, R. M. (Tennessee Mid-South Regional Med. Program, Nashville) and Y. C. Ho. *Cancer* 29(5):1264-1267, 1972.

This study focuses on the rate and types of cancer occurring in relatives of persons with hepatomas. Retrospective review of death certificates in Nashville for a 17-yr period provided 53 cases of patients dying of primary cancer of the liver, and contact was successfully made with their respondents. A control group of 48 cases (death due to accident or coronary disease) was established. In the hepatoma cases, death certificates for 30 parents and siblings out of 319 listed cancer as the cause of death, while in the control group 8 out of 295 had cancer listed as the cause of death. Numbers of cancers occurring for fathers, mothers and brothers of hepatoma patients were significantly higher than in the control group. Interestingly, there was no significant difference of cancer incidence between sisters of hepatoma patients and of controls. A relative frequency of sites for males included lungs, prostate gland, large intestine and stomach. In females, the greatest frequency occurred in breast, cervix, large intestine and ovaries. Recommendation is made for additional studies on familial factors and unknown environmental conditions.

- 2860 CHARACTERISTICS OF CELL PROLIFERATION IN ACUTE LEUKEMIA. (E.) W. H. Cheung, (Long Island Jewish Med. Ctr., New York), K. R. Rai and A. Sawitsky. *Cancer Res* 32(5):939-942, 1972.

An autoradiographic procedure for early detection of nonresponse to chemotherapy in cases of acute leukemia is described. Bone marrow aspirates and venous blood samples from 26 acute lymphoblastic leukemia patients and 10 normal controls were used for testing. A gross number of bone marrow cells ranging from  $5$  to  $8 \times 10^6$  was labeled with  $5 \mu\text{Ci}$  of tritiated thymidine. When peripheral blood was used the leukocyte count was adjusted to match that of aspirates. Cell suspensions were incubated for 2 hr, centrifuged at 800 rpm for 10 min, and the cells were washed with physiologic saline. Cells were smeared on gelatin-coated slides, with five smears prepared from each culture. Background for nonlabeled cells was less than three grains; labeled cells contained at least 20 grains. The number of labeled cells/100 nonerythroid nucleated cells provided an estimate of the population, which was in the DNA synthesis phase of the generative cycle. Thus an index of the proliferation cell population could be determined. Analysis of samples indicated that the number of proliferating cells in leukemics during relapse was significantly smaller than in controls. In 13 patients there was a marked increase in the number of proliferating cells from bone marrow early in the course of therapy; all patients responded to treatment. These findings indicate that this technique is a reliable indicator of patient response to treatment early in the course of chemotherapy, and as such would be

invaluable for indicating a change in the therapeutic approach before onset of toxicity.

- 2861 SPONTANEOUS ENDOCRINE TUMORS IN MASTOMYS. (E.) Fujii, K. (Natl. Inst. Hygienic Sci., Tokyo, Japan) and H. Sato. *Gann* 63(1):135-137, 1972.

This report deals with tumors observed in the endocrine glands of the tumor-prone mastomys (*Praomys natalensis*). The characteristics, origin of the mastomys colony and tendency to produce spontaneous tumors at various body sites were given in an earlier report. A total of 158 animals (76 male and 82 female) are examined and tumors occurring in the endocrine glands removed and prepared for histologic examination. The tissues prepared included six pituitary, three reproductive and 13 adrenal tissues. The age of the animals developing these primary growths was between 36 and 127 weeks. Result of histologic examination showed the tumor tissues to be benign; this conclusion was drawn because of a lack of invasiveness and metastasis. The process of spontaneous tumor development in these animals is attributed to endocrine imbalance, hormonal imbalance and possible genetic involvement. Continued investigations are being carried out to determine the causal factors involved.

- 2862 METASTATIC TUMORS OF THE SKIN. (E.) Brownstein, M. H. (Armed Forces Inst. Path., Washington, D.C.) and E. B. Helwig. *Cancer* 29(5):1298-1307, 1972.

An analysis of cutaneous metastasis occurring in 724 patients is presented. The primary tumors included carcinoma occurring at all sites but most frequently found in the lungs, intestines, melanoma, oral cavity and kidneys. In reviewing patients treatment records it was noted that the secondary cutaneous lesion was recognized before the primary lesion was found in the case of kidney and lung. In contrast, secondary lesions in women with breast cancer were identified subsequent to the identification of the primary breast tumor. Analysis of these lesion sequences is considered valuable to patient prognosis, indicating that specific trends exist between cutaneous sites and the location of the primary tumor. Examples of these relationship incidences are: 1) metastases from breast tumor to anterior chest wall; 2) metastases from carcinoma of the intestine to the skin of the abdomen; and 3) metastases to the ear and neck from cancer of the oral cavity. Additionally, it was noted that cancers tending to invade lymphatic channels appear late in the course of the disease, overlying the area of the primary tumor.

2863 SEX CHROMATIN IN GYNECOLOGIC CANCER: INCIDENCE AND LIMITATION OF ITS CLINICAL INTERPRETATION. (E.) Siracky, J. (Cancer Res. Inst., a, Bratislava, Czechoslovakia). *Acta Cytol* 16(2): 105-110, 1972.

The incidence of sex chromatin in cells from various gynecologic cancers in 651 cases treated from 1953 to 1965 was determined in Feulgen-stained histologic sections. Cases with an average occurrence ranging from 0-9% were classified as sex chromatin negative and cases with values of 20% or more, as sex chromatin positive. Nuclear size measurements were performed by micrometer estimation on Feulgen stained sections from cases of epidermoid cancer of the cervix (characterized by variations in ploidy with frequent polyploid cell groups) and endometrial cancer (predominantly near diploid). Nuclear size  $<10\mu$  was considered as near diploid and  $>10\mu$ , as polyploid. The five year survival rate of the 162 patients with sex chromatin negative cancers was, in general, worse than that of the 489 cases with sex chromatin positive malignancies. The five year survival rate was lower (47%) in patients with sex chromatin positive cervical cancer treated with radiation than that of the corresponding group treated surgically (65%). Patients with sex chromatin negative cervical cancer treated either surgically or with radiation had about the same five year survival rate (38 and 35%, resp.). No difference in five year survival rate was seen between patients with sex chromatin positive or negative uterine cancer treated surgically (59 and 58%, resp.). The five year survival rate for patients with sex chromatin positive uterine cancer treated by radiation (45%) was almost twice as high as that of patients with sex chromatin negative uterine cancer (26%) treated in the same manner. A comparison of the histological grade of epidermoid and endometrial cancers with the incidence of sex chromatin indicated that the cancers which were sex chromatin negative were predominantly poorly differentiated (53 to 70%). Sex chromatin negative nuclei in endometrial cancer were on the average somewhat larger than sex chromatin positive nuclei. The greatest degree of variation in size was seen in poorly differentiated epidermoid cancer and was explained on the basis of a higher incidence of polyploid cells in the sex chromatin negative group. Considering the possibility of various types of sex chromatin negativity, it was concluded that the explanation of prognostic differences on cytogenetic basis alone does not seem to be sufficient and valid for all tumor types and degrees of differentiation.

2864 ISOLATION AND CHARACTERIZATION OF RIBOSOMES FROM L5178Y MOUSE LYMPHOMA CELLS. (E.) Murty, C. N. (U. Alberta Cancer Res. Unit Edmonton, Canada) and T. Tamaoki. *Arch Biochem* 149 (1):281-288, 1972.

This investigation presents a detailed preparative procedure for the lymphoma ribosomes and discusses some of their physical and biological properties. Cells used for this experiment are L5178Y lymphoma cells extracted from ascitic fluid in the abdominal cavity of male BDF mice. All buffers employed in

the extraction of the ribosomes contained 20 mM Tris-HCl, pH 7.4, 6 mM  $\beta$ -mercaptoethanol, 0.5 mM dithioerythritol and 10% glycerol. In addition, the following components were present: 1) Buffer A: 2 mM  $Mg^{2+}$ , 100 mM KCl; 2) Buffer B: 5 mM  $Mg^{2+}$ , 100 mM KCl; 3) Buffer C: 1 mM  $Mg^{2+}$ , 100 mM KCl; and, 4) Buffer D: 10 mM  $Mg^{2+}$ , 1 M KCl. Cells at a concentration of  $50 \times 10^6$  cells/ml were suspended in buffer A and disrupted with glass beads, then centrifuged. This procedure was serially repeated until all large aggregates were removed. A final suspension was dialyzed overnight against buffer A. The "crude ribosomes" obtained were treated with buffer D for 30 min at  $0^\circ$ , centrifuged, then resuspended with buffer D and were once more dialyzed against buffer B. The ribosomes thus prepared are referred to as "KCl-ribosome". Purification of crude ribosomes was achieved by passing the materials suspended in buffer D through a DEAE-Sephadex column and subsequently through sucrose solutions. The ribosomes were generally eluted as a single broad peak. Ribosomal denaturation was prevented by using buffer D. The high content KCl in the procedure caused dissociation of 80S ribosomes into 40S and 60S subunits. Reassociation was accomplished by reducing the KCl content. The polypeptide-synthesizing abilities of the ribosome preparations were determined by using poly U-directed phenylalanine incorporation. Estimates indicated the incorporation reached 20-30 pmoles/ $A_{260}$  or 300-450 pmoles/mg ribosomes. Tests showed that DEAE-sephadex ribosomes" and "KCl-ribosomes" could be stored at  $0^\circ$  for at least one week without losing amino acid incorporating ability.

2865 MITOCHONDRIAL DNA OF HUMAN-MOUSE CELL HYBRIDS. (E.) Clayton, D. A. (City of Hope Natl. Med. Ctr., Duarte, Calif.), R. L. Teplitz, M. Nabholz, H. Dovey and W. Bodmer. *Nature* 234(5331):560-562, 1971.

Six human-mouse hybrid cell lines were examined. Mitochondrial DNA (M-DNA) was isolated at several different generations after hybridization by previously reported methods and the number of human chromosomes was determined from karyotypes prepared at the time of M-DNA analysis. Density gradients of M-DNA preparations from these six hybrids revealed only mouse M-DNA. Electron microscope examination of each of the M-DNA samples showed more than 98% of the DNA present was circular and of a form consistent with that isolated from a variety of mouse cells. No hybrid or aberrant forms of circular DNA occurred. It is believed that a mixed population of mitochondria are present at the time of cell fusion, but that the human mitochondria were either not propagated or more slowly propagated than the mouse mitochondria.

2866 REGULATION OF ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE METABOLISM IN CULTURED NEUROBLASTOMA CELLS. (E.) Gilman, A. G. (Natl. Inst. Hlth., Bethesda, Md.) and M. Nirenberg. *Nature* 234(5328):356-358, 1971.



The effect of various chemical agents on adenosine 3',5'-cyclic monophosphate (cAMP) levels in clonal lines of cultured mouse neuroblastoma C-1300 cells was studied. Experimental cells were preincubated 60 min in serum-free medium containing theophylline (1.0 mM). Compounds to be tested were added and cells were incubated an additional 15 min at 37°C. Cyclic AMP (cAMP) was extracted with 5% trichloroacetic acid. Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>,  $2.9 \times 10^{-6}$  M) without theophylline, elevated intracellular cAMP levels after as little as one sec exposure to cells (30 pmoles cAMP/mg protein). The rapidity of change of intracellular cAMP levels suggested that local changes in cAMP could occur fast enough to mediate rather short latency effects of neurotransmitters. Maximal cAMP levels were attained by 5 to 15 min (120 to 200 pmoles/mg protein). Cells maintained intracellular cAMP levels >100 pmoles/mg protein for 24 hr. Theophylline potentiated the effect of PGE<sub>1</sub> two- to three-fold. Although PGE<sub>1</sub> was the most effective, PGE<sub>2</sub> showed definite activity (50-80 pmoles/mg protein) and the effect of PGE<sub>1</sub> at  $2.9 \times 10^{-6}$  M was probable (50 pmoles/mg protein). While theophylline had no effect on cell multiplication, PGE<sub>1</sub> plus theophylline virtually prevented accumulation of cells.

- 2867 SELECTIVE GROWTH OF HUMAN NEOPLASTIC CELLS IN MEDIUM LACKING SERUM GROWTH FACTOR. (E.) Scher, C. D. (Natl. Cancer Inst., Bethesda, Md.) and G. J. Todaro. *Exp Cell Res* 68(2):479-481, 1971.

A study of the growth of human neoplastic cells in medium containing factor-free serum is presented. Human cells from tumor explants of a rhabdomyosarcoma (130T), an osteosarcoma (131T), a bronchogenic carcinoma (9812), whole human embryos (HEM), adult fibroblasts, human embryonic kidney and HeLa cells were used. All cultures (except embryonic kidney cells which were tested as a primary culture) were passed one to 30 times in complete medium before being transferred ( $5 \times 10^4$  cells per 50 mm plastic plate) into medium containing agamma newborn calf serum (10%) prepared by heating at 70°C for 30 min. Controls were maintained in complete medium and plates containing medium were changed in all cultures at biweekly intervals. All cell lines of human tumor explants grew in both factor-free and complete medium, reaching densities of from  $3 \times 10^6$  (130T) to  $2 \times 10^7$  cells/plate. Growth patterns were disoriented. A suspension culture of a mammary adenocarcinoma (F230) was also passed successfully in factor-free medium. Nonmalignant cell lines grew in complete medium to densities of from  $7 \times 10^5$  to  $2 \times 10^6$  cells/plate, but showed little or no growth in factor-free medium. It is concluded that factor-free medium may be used to isolate human neoplastic cells which exhibit low saturation density and unchanged morphology.

- 2868 SURFACE GLYCOPROTEIN CHARACTERISTIC OF THE DIFFERENTIATED STATE OF NEUROBLASTOMA C-

1300 CELLS. (E.) Brown, J. C. (Lab. Molecular Biol., Cambridge, England). *Exp Cell Res* 69:440-442, 1971.

Cell surface glycoprotein components were examined from undifferentiated and differentiated cells after exposing growing neuroblastoma C-1300 clone I cells for two days to tritiated glucosamine. Differentiated morphologic expression was promoted by addition of  $8 \times 10^{-6}$  M 5-bromodeoxyuridine (BUDR) to the culture medium. Glycopeptides obtained from the cells were fractionated by DEAE cellulose column chromatography into four components eluting at 0.03 M, 0.04 M, 0.06 M and 0.07 M NaCl. These are called glycopeptides 1, 2, 3 and 4, resp. Undifferentiated neuroblastoma cells had glycopeptides 3 and 4 but not 1 and 2, while differentiated cells contained glycopeptide 1 as well as 3 and 4. It was found that addition of  $4 \times 10^{-5}$  M thymidine to the culture medium resulted in decreased expression of glycopeptide 1 corresponding to a decrease in the percentage of differentiated cells; this effect was also seen when cells were grown without BUDR. It is suggested that BUDR influences a pre-existing balance between undifferentiated and differentiated cells.

- 2869 UMBILICAL CORD LEUCOCYTES TRANSFORMED BY LYMPHOID CELL FILTRATES FROM HEALTHY PEOPLE. (E.) Chang, R. S. (Dept. Med. Microbiol., U. California, Davis). *Nature* 233(38):124, 1971.

It has been found that a cell-free filtrate of lymphoid cell lines from healthy individuals was able to effect transformation of umbilical cord blood leucocytes. Four cell lines (RM3, AM262, JR1 and KF21) were obtained from healthy individuals who were positive for Epstein-Barr virus (EBV) antibody; RM3 and AM262 were found negative for EBV antigens using the indirect immunofluorescent test. The concentrated cell suspension was frozen and thawed five times and then filtered. The cell-free leucocyte filtrate was added to a cell-free filtrate of umbilical cord blood leucocytes. Control cord blood leucocyte cultures did not transform spontaneously while some cultures treated with filtrates of AM262, RM3 and JR1, but not KF21, transformed. Two cord blood leucocyte lines were found positive for EBV antigens after transformation by AM262 and RM3 cell-free filtrates. It is postulated that the presence of these EBV antigens indicates that infectious EBV or an EBV antigen-inducing agent may be present in the cell-free filtrate.

- 2870 LUNG CANCER AS AN ENDOCRINE DISEASE. (E.) Rao, L. G. S. (Southern General Hosp., Glasgow, Scotland). *Nature* 235(5335):220-222, 1972.

Investigations were carried out to determine whether hormones are related to lung cancer development; measurements were made of the content of individual and total 17-oxosteroids and total 17-

hydroxycorticosteroids (17-OHcs) in the urine of patients and controls. The connection between steroid abnormalities and lung cancer was found to be high enough to be of diagnostic value; the association between cigarette smoking and lung cancer was far less significant. Because steroid abnormalities were still found after lung tumor removal it was concluded that they were not produced by the presence of the lung tumors. Considerably greater amounts of androsterone and 17-OHcs were found in the urine of lung cancer patients than in normal men. Experimental results indicated that androsterone concentrations were not correlated with the stage of the disease. It is suggested that administration of androsterone or a suitable precursor might be of therapeutic value for lung cancer patients.

- 2871 ON THE DIRECTION OF READING OF BACTERIOPHAGE T4 GENE 43 (DEOXYRIBONUCLEIC ACID POLYMERASE). (E.) O'Donnell, P. V. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.) and J. D. Karam. *J Virol* 9(6):990-998, 1972.

Amber (*am*) mutants of the two closely linked sites, B22 and C125, in bacteriophage T4 gene 43 (DNA polymerase) have been shown in the nonpermissive (*su*<sup>-</sup>) *E. coli* host to synthesize gene 43 products which are devoid of DNA polymerase activity, but which retain their 3'-exonuclease activity. DEAE-cellulose chromatography of DNA polymerase and DNase activities from nonpermissive *su*<sup>-</sup> cells infected with single- and double-*am* mutants of T4 gene 43 showed that the exonuclease activity which was observed with *am*B22 was not seen with double mutants carrying, in addition to *am*B22, *am* mutations which mapped to the clockwise side of the B22 site on the circular genetic map of T4. Similarly, *am* mutations which mapped to the clockwise side of the C125 site abolished the exonuclease activity which was observed with the *am* mutant (*am* E4335) of this site. It was concluded that in these double mutants, termination signals to the clockwise side of *am*B22 and *am*E4335 were encountered before the *am*B22 and *am*E4335 signals during translation of the messenger RNA from T4 gene 43. Thus, it seems that the T4 DNA polymerase is synthesized *in vivo* in a direction which corresponds to a counterclockwise reading of gene 43.

- 2872 MAMMARY CARCINOMA: A SPECIFIC BIOCHEMICAL DEFECT IN AUTONOMOUS TUMORS. (E.) McGuire, W. L. (U. Texas Med. Sch., San Antonio), K. Huff, A. Jennings and G. C. Chamness. *Science* 175(4019):335-336, 1972.

Rat mammary carcinoma (R3230AC) has a non-regression characteristic following ovariectomy; *in vitro* studies are completed using chromatin prepared from R3230AC tumor nuclei with and without estradiol binding protein (EBP) to verify this fact. For testing purposes, the ratios of histone protein to DNA and that of nonhistone protein to DNA were 0.90 to 1.72

and 1.11 to 1.42 respectively. Cytosol fractions from rat muscle, brain, uterus and R3230AC tumor were prepared from the 105,000g supernatant of tissue homogenates and incubated with 17 $\beta$ -[6,7-<sup>3</sup>H]estradiol for 60 minutes at 4 C. The complex of <sup>3</sup>HE<sub>2</sub> and cytoplasm from R3230AC tumor, muscle and brain failed to bind to R3230AC chromatin. This lack of binding ability is attributed to the lack of EBP. To substantiate this result additional testing of rat uterine cytosol, which has abundant EBP, was completed. Analysis of test results in both phases of the experiment showed that EBP is lost during neoplastic transformation, and it is proposed that this loss inhibits normal estrogen action in tissues. Identification of the specific component in EBP which participates in this interaction has not been made.

- 2873 CHARACTERISTICS OF AVIAN TRANSMISSIBLE LYMPHOID TUMOR CELLS MAINTAINED IN CULTURE. (E.) Siegfried, L. M. (Dept. Vet. Sci., U. Wisconsin, Madison) and C. Olson. *J Nat Cancer Inst* 48(3):791-795, 1972.

Avian transmissible lymphoid tumors (TLT) growing in muscle of White Leghorn chickens were used as a source of cells for continuous suspension cultures. Electron microscopic observation of cultured cells indicated that they were poorly differentiated. Nuclear shape varied considerably. The chromatin was generally very fine and evenly dispersed. Nucleoli were well-defined and often bizarre in shape. Many mitochondria and free ribosomes were evident in the cytoplasm and the sparse endoplasmic reticulum was usually of the rough type. Type-C particles, resembling those described in the avian leukosis/sarcoma complex, were common, especially in extracellular spaces. Particles were also frequently seen within cytoplasmic vacuoles, and occasionally budding from the outer cell membrane. Six of the cell lines were maintained in culture for over 280 days and retained antigenic properties characteristic of the original transmissible tumor cells. I.m. and i.p. inoculation of cultured tumor cells into day-old Line 15 I chicks produced local and visceral tumors similar to those produced by TLT cells.

- 2874 PURE-STRAIN AND GENETICALLY MOSAIC LIVER TUMORS HISTOCHEMICALLY IDENTIFIED WITH THE  $\beta$ -GLUCURONIDASE MARKER IN ALLOPHENIC MICE. (E.) Condamine, H. (Inst. Cancer Res., Philadelphia, Pa.), R. P. Custer and B. Mintz. *Proc Nat Acad Sci USA* 68(9):2032-2036, 1971.

Hepatocarcinogenesis was analyzed *in situ* by applying a histochemical method for visualization of the enzyme  $\beta$ -glucuronidase to tissue sections from allophenic mice. The animals had a lifelong genetic mosaicism for cells with the allele for low  $\beta$ -glucuronidase activity (*g/g* genotype, C3H strain) and cells with the allele for high



activity (G/G genotype, C57Bl/6 or Balb/c strain). The former strain is also hepatoma-susceptible; both the latter are nonsusceptible. Twelve "spontaneous" hepatomas were examined by histochemical visualization of  $\beta$ -glucuronidase and biochemical genotypic analyses of the liver proteins. Nine of the 12 were made up entirely of susceptible-strain hepatic cells and one was of the nonsusceptible strain. That the lack of staining in these nine truly reflected cell genotype and was not due to switching off of  $\beta$ -glucuronidase synthesis during tumorigenesis was demonstrated by the biochemical results: all five hepatomas in the group analyzed with the Mdh-1 marker showed only the C3H electrophoretic variant. Both histochemical and biochemical data on normal liver parts revealed that most of the pure-strain hepatomas arose in livers with some genotypic admixture of cells. Five of these hepatomas arose in individual lobes containing cells of both genotypes with both normal cell strains sometimes present at the very margin of the single-genotype tumor. The most striking result appeared in two hepatomas where both unstained and  $\beta$ -glucuronidase stained cells, both apparently malignant, were found. It appears consistent with the pure-strain results to interpret the mosaically stained tumors as mixtures of C3H and C57Bl/6 cellular genotypes. The mere existence of mosaic tumors indicates that a hepatoma, even in a single-genotype animal, should be conceived of as a genetically complex entity that may well comprise disparate clones of transformed cells rather than a uniform pure clone.

- 2875 NUCLEOTIDE SEQUENCE OF 4.5 S RIBONUCLEIC ACID OF NOVIKOFF HEPATOMA CELL NUCLEI. (E.) Ro-Choi, T. S. (Baylor Coll. Med., Houston, Texas), R. Reddy, D. Henning, T. Takano, C. W. Taylor and H. Busch. *J Biol Chem* 247(10):3205-3222, 1972.

The primary sequence of nucleotides was defined for *in vitro*  $^{32}\text{P}$ -labeled 4.5 S RNA<sub>1</sub>, one type of low-molecular-weight nuclear RNA of Novikoff hepatoma ascites cells. 4.5 S RNA was purified by sucrose density centrifugation, polyacrylamide gel electrophoresis and DEAE-Sephadex A-50 column chromatography. Nucleotide sequences were identified by paper chromatography of various RNase and phosphodiesterase hydrolysates. RNA was shown previously to be specifically localized in the extranucleolar portion of the nucleus. It was not a precursor to tRNA. The primary sequence of nucleotides, of which there were 96, showed a purine-rich 5' and a pyrimidine-rich 3' end: pppG-G-U-C-G-A-G-A-G-G-A-U-G-G-C-U-C-A-G-C-C-G-U-U-A-A-A-G-G-C-U-A-G-G-C-C-A-A-A-A-U-A-A-C-A-C-C-U-A-U-A-A-G-A-G-U-U-C-G-G-U-U-C-C-C-A-G-C-A-C-C-A-C-G-G-C-U-G-U-C-C-U-U-C-C-A-G-C-A-C-C-U-U-U-OH.

- 2876 CYTOLOGICAL AND CYTOGENETICAL STUDIES ON BRAIN TUMORS: IV. IDENTIFICATION OF THE

MISSING G CHROMOSOME IN HUMAN MENINGIOMAS AS NO. 22 BY FLUORESCENCE TECHNIQUE. (E.) Zankl, H. (Max-Planck Inst. Psych., Munich, Germany) and K. D. Zang. *Humangenetik* 14(2):167-169, 1972.

Previous reports have shown that one G group chromosome is regularly missing in human meningiomas. Five meningiomas were studied by atebri-ne-acetic acid fluorescence staining to determine if the same chromosome was lost in each case. In all five cases the weaker-staining, longer, G group chromosome identified as number 22 was missing. Five of more than 70 meningiomas previously studied contained a Ph<sup>1</sup>-like chromosome deletion. One of the five cases studied by fluorescence staining also showed an accessory stemline bearing a Ph<sup>1</sup>-like chromosome identified as a deleted number 22. Similarities between the cytogenetic patterns observed in these meningiomas and those reported for chronic myeloid leukemic cells suggest that the distal part of chromosome 22 may bear information involved in the control of cell proliferation.

- 2877 EVALUATION OF THE MODE OF CELL DEATH IN EHRlich ASCITES TUMOR. (E.) Lala, P. K. (Dept. Anat., McGill U., Montreal, Quebec, Canada). *Cancer* 29(1):261-266, 1972.

Experiments were conducted to determine whether cell death in mouse Ehrlich ascites tumor preferentially affected the nonproliferating or the proliferating population and to determine whether there was any cell death connected with mitosis. Ehrlich ascites tumor was grown by a routine weekly transfer of  $10^6$  tumor cells in the peritoneal cavity of CF<sub>1</sub> female mice of 10-12 wk of age and the kinetics of cell loss in the seven day tumor was evaluated by repeated labeling with  $^3\text{H}$ -thymidine ( $^3\text{HTdR}$ ), combined with the measurements of cell cycle characteristics by the labeled mitosis technique after a single injection of  $^3\text{HTdR}$ . The median cell cycle time was 24 hours (S period = 20 hours, G<sub>2</sub> + mitosis = 4 hours, and there was no measurable G<sub>1</sub>), and the rate of cell production approached the rate of cell loss at this stage. The absence of G<sub>1</sub> was verified with a double-labeling technique. On the basis of these data, the temporal changes in the labeling indices of tumor cells, tumor cells in mitosis, and figures resembling degenerating mitoses following repeated  $^3\text{HTdR}$  injection could be best explained by an age-specific elimination of non-cycling cells and a small amount of mitotic death.

- 2878 MITOSIS IN HUMAN LEUKEMIC LEUKOCYTES DURING COLCEMID INHIBITION AND RECOVERY. (E.) McGill, M. (Dept. Biol., U. Texas, Houston) and B. R. Brinkley. *Cancer Res* 32(4):746-755, 1972.

Cultured peripheral leukocytes from five chronic (CML) and two acute (AML) myelogenous leukemia patients and PHA-stimulated lymphocytes from healthy

donors were treated with Colcemid (0.02  $\mu\text{g/ml}$ , two hr) to arrest dividing cells in metaphase. Upon removal of Colcemid, normal lymphocytes progressed through mitosis within 120 min. Electron microscopic observation showed that, as in other mammalian cells, Colcemid inhibited the migration of centriole pairs to opposite poles in both normal and leukemic cells and resulted in the formation of a unipolar spindle with chromosomes displaced radially about the centrioles (C-mitosis). Upon removal of Colcemid, the centriole pairs moved apart and a normal bipolar spindle was formed. The recovery of CML cells from Colcemid block proceeded at a much slower rate than normal lymphocytes. The percentage of telophase cells at 120 min was low and most cells at this time were still in metaphase. Mitotic abnormalities, such as multipolar spindles, anaphase bridges, and lagging chromosomes, were evident in some cells. Cells from three cultures derived from one AML patient failed to recover from Colcemid inhibition. Leukemic leukocytes recovering from Colcemid block showed abnormal centriole structure and migration.

- 2879 INHIBITION OF ASCITES TUMOR DEVELOPMENT BY CONCANAVALLIN A. (E.) Inbar, M. (Weizmann Inst. Sci., Rehovoth, Israel), H. Ben-Bassat and L. Sachs. *Int J Cancer* 9(1):143-149, 1972.

The toxicities and agglutinating abilities of concanavalin A (ConA), which binds to glucose- or mannose-like sites on the cell surface membrane, and wheat germ (WGA) and soybean (SBA) agglutinins, which bind to N-acetyl-D-glucosamine-like and N-acetyl-D-galactosamine-like sites, resp., were studied *in vivo* and *in vitro* on an ascites form of a Moloney virus-induced lymphoma (YAC). Although YAC cells were agglutinated by all three agglutinins, only ConA (62.5-500  $\mu\text{g/ml}$ ) showed a marked toxic effect when injected i.p. into A mice which had been inoculated with YAC cells. *In vitro* incubation of YAC cells with 125  $\mu\text{g}$  ConA/ml for 34 hr lysed 95% of the cells. I.p. injection of 1 mg ConA at one hr, two days and five days after i.p. inoculation of  $10^2$  YAC cells into adult A mice, resulted in an inhibition of tumor formation in 70, 50 and 20% of the animals, resp. The toxic effect of ConA on YAC cells *in vivo* and *in vitro* and the lack of such toxicity by WGA and SBA indicated that activities essential for cell survival were associated with ConA sites, but not with sites for the other two agglutinins.

- 2880 NON-HODGKIN'S LYMPHOMAS: I. BONE MARROW INVOLVEMENT. (E.) Jones, S. E. (Stanford U. Med. Ctr., Calif.), S. A. Rosenberg and H. S. Kaplan. *Cancer* 29(4):954-960, 1972.

Bone marrow involvement in 218 cases of malignant lymphoma (non-Hodgkin's lymphoma), classified according to the scheme of Rappaport et al., was investigated between 1960-1970. Bone marrow was obtained by aspiration, needle biopsy, open bone mar-

row biopsy or by various combinations of the three. A histologically positive bone marrow was defined as unequivocal evidence of lymphoma in the marrow. Open marrow biopsy demonstrated lymphoma after needle biopsy was negative, and both biopsy techniques were clearly superior to bone marrow aspiration in identifying marrow involvement. Bone marrow involvement correlated with advanced stage, cellular composition of the lymphoma, and, in the nodular lymphomas, splenomegaly and constitutional symptoms. Patients with histiocytic lymphomas uncommonly had initial marrow involvement whereas patients with mixed and lymphocytic types were frequently affected. Nodular or diffuse patterns did not influence the incidence of marrow involvement, but patients with nodular lymphomas and positive marrows survived significantly longer than those with diffuse lymphomas.

- 2881 THE TOPOGRAPHY OF SOME ANIONIC SITES AT THE SURFACES OF FIXED EHRLICH ASCITES TUMOUR CELLS. (E.) Weiss, L. (Roswell Park Memorial Inst., Buffalo, N.Y.), O. S. Jung and R. Zeigel. *Int J Cancer* 9(1):48-56, 1972.

The distribution of positively charged, colloidal iron hydroxide particles to the surfaces of glutaraldehyde-fixed Ehrlich-Létré ascites tumor (EAT) cells was studied in 700 Å thick sections with the electron microscope. After incubation with neuraminidase and/or ribonuclease A, and fixation, cells were also reacted with particles. Treatment of EAT cells with neuraminidase and ribonuclease, which had previously been shown to reduce the densities of anionic sites at the cell surface, almost totally prevented binding of particles. Treatment with neuraminidase alone ( $10 \text{ U}/10^7$  cells) was also effective, causing an 86% reduction in binding compared with controls. Ribonuclease treatment alone ( $0.2 \text{ mg}/10^7$  cells) produced only a 25% reduction in binding. Statistical analysis of binding patterns indicated that binding on control and on ribonuclease-treated cells followed a Poisson distribution. Particles on the surface of neuraminidase-treated cells, however, were arranged in clusters, but the clusters themselves were arranged in a Poisson distribution. The data were tentatively interpreted as indicating the presence of different-sized neuraminidase- and ribonuclease-susceptible zones at the cell surface, having a higher than average density of anionic sites.

- 2882 CONTINUOUS LYMPHOBLASTOID CELL LINE FROM A RHESUS MONKEY WITH MYELOGENOUS LEUKEMIA. (E.) Dunkel, V. C. (Natl. Cancer Inst., Bethesda, Md.) and S. L. Myers. *J Nat Cancer Inst* 48(3):777-782, 1972.

A suspension culture was initiated from the peripheral leukocytes of a rhesus monkey with myelogenous leukemia and was designated LM/DM. The cells did not



- form monolayers in culture. Morphologically, the cells resembled those lymphoblastoid cells in culture derived from human leukocytes. The generation time for logarithmically growing LM/DM cells was 28-32 hr. No herpes or other virus particles were seen in cells inspected by electron microscopy. Chromosome analysis revealed the modal number to be 42. Indirect immunofluorescence tests on acetone-fixed and viable LM/DM cells and complement fixation tests on cell extracts indicated that the cells contained no Epstein-Barr virus (EBV) or EBV-related antigens.
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